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MEGALOCYTIC DEFICIENCY ANAEMIA CURED BY SMALL AMOUNTS OF FRESH ENDIVE

BY

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(RECEIVED FOR PUBLICATION OCTOBER 21, 1951)

Megalocytic anaemia in childhood is an unusual disease in The Netherlands. Routine examination of the bone marrow of anaemic patients rarely reveals the existence of this type, and is probably due to an adequate number of clinics, which give advice to the majority of the mothers on the infant's diet during the first year of life. The continued functioning of these clinics during the German occupation may explain the absence of an increase of the anaemias during that period. During the last 10 years we have seen only four patients, in whom an exclusive diet of goat's or cow's milk led to the development of dystrophy and megalocytic anaemia at the age of about 1 year. Attention was drawn to this form of anaemia with its characteristic bone marrow findings (Veeneklaas, 1940, 1942). At that time it was possible to prove that fresh vegetables and/or fresh fruit contained substances which were able to cure this anaemia. It was shown (Veeneklaas, 1943 and 1947), and in 1949 and 1950 it was confirmed, that these substances were present in fresh endive.

Megalocytic anaemia had been described before. In 1909 von Starck published the first case, and Faber and Bachman in 1928 and 1936 were able to collect 20 cases from the literature. Meanwhile the fact was noticed that these children often suffered from infections of the upper respiratory tract and sometimes had diarrhoea, and liver therapy caused a reticulocyte crisis and recovery without relapse. Later folic acid (Zuelzer and Ogden, 1946) and vitamin B_{12} (McPherson, Jonsson and Rundles, 1949) were found to exert the same influence. The pathogenesis of these anaemias is still uncertain. Somewhere in the chain of supply, absorption, transport, storage, liberation, consumption and excretion of the anti-anaemic substances a link may drop out, which is not necessarily always the same.

Case Reports

Case 1. The normal pregnancy of a healthy primiparous woman ended on December 21, 1937, in the birth of a normal child weighing about 3,000 g. The child was breast-fed for six weeks, and was then put on cow's milk, with the addition of water and sugar and later flour, in the correct amounts. After six months he was given cooked vegetables in the milk formula. Until the eighth month he developed well, but at that time anorexia started and pallor was noted. At the age of 12 months he had pneumonia and the haemoglobin was 45%. Treatment with iron and ascorbic acid in large doses did not influence either the anorexia or the anaemia. The child lived in an institution, which for 16 years had taken care of 70 children a year in a similar way. A syndrome such as that described had never occurred in the home during the whole time.

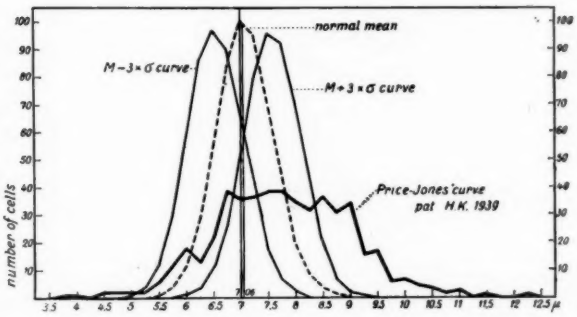

FIG. 1.—Case 1. Price-Jones curve.

In March, 1939, the child was admitted to hospital. At the age of 15 months the patient was 70 cm. tall and weighed 6,600 g. There was marked dystrophy, apathy and pallor. On the forehead and on the temples there was a thick growth of downy hair. The lymph nodes were all just palpable; the mouth and tongue showed no abnormalities. The heart and lungs seemed normal. The liver and spleen could be felt. Values for free and total acidity were: fasting, 0/30, after one hour, trace /10, after two hours, 10/22.

Haemoglobin was 42%, erythrocytes were 1,650,000 per c.mm. There was anisocytosis, poikilocytosis and polychromasia. The colour index was 1·3. A Price-Jones curve (Fig. 1) demonstrates the size of the erythrocytes. Reticulocytes were 0·7% and leucocytes 7,150/c.mm., of which 5,400 were lymphocytes. Thrombocytes were 38,000/c.mm. and the bilirubin level was 0·74 mg.%. Fragility started at 0·45%, and was

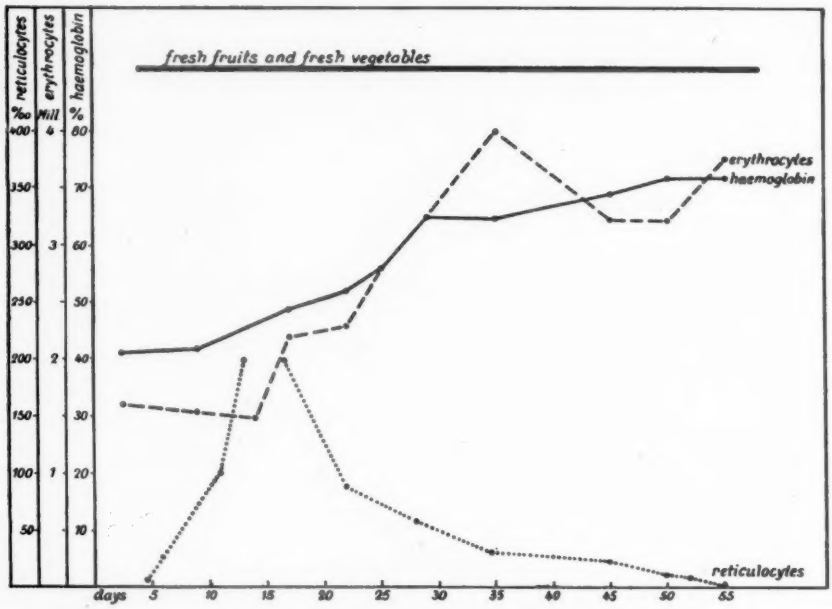

FIG. 2.—Case 1. Reticulocyte crisis and improvement in blood count.

complete at 0·32% Na. Cl. The bone marrow picture was megaloblastic. Treatment consisted of the addition of large amounts of fresh vegetables and fresh fruit to the diet which the child previously had. After 10 days a reticulocyte crisis of over 20% followed (Fig. 2). After four weeks the haemoglobin was 66%. Ten weeks later the weight had increased to 9,000 g., the downy hair had disappeared, liver and spleen were no longer palpable, haemoglobin was 80%, erythrocytes 4,540,000/c.mm., leucocytes 9,850/c.mm., of which 5,320 were lymphocytes. The bone marrow picture had become completely normal. Relapse did not occur.

Evaluation of the treatment was made difficult by the addition of more than one green vegetable to the original diet.

Case 2. In June, 1941, a healthy mother was delivered of her first child, a girl, who was normal and weighed 3,250 g. The child was immediately put on a cow's milk formula with the correct addition of water, sugar and flour. The parents were intelligent people, who would have given their child a complete diet but who, as Jews during the German occupation, were restricted in their movements. The only possible supplementary food was the juice of preserved endive, which was given sporadically after the sixth month. Infections did not occur. Development was normal until the ninth month, then anorexia started and pallor was noted. The child was given iron and ascorbic acid but without effect. At the time of treatment in 1942 the patient was 11 months old; the height was 71 cm., but the weight was unknown because there were no scales at home. The patient was a markedly dystrophic, apathetic child with a flabby skin and intense pallor. A few lymph nodes were palpable in the neck and the inguinal region. Nothing abnormal was noted in the mouth, tongue, heart or lungs. The liver and spleen were just palpable. Values for free and total acidity were: fasting 15/20, and after half hour 25/35. The blood bilirubin level was 0·8 mg.%. Fragility began at 0·46 and was complete at 0·34% Na. Cl. The faeces contained 26% fat. Haemoglobin was 28%, erythrocytes were 1,090,000/c.mm., and there was anisocytosis, poikilocytosis and anisochromia. The colour index was 1·28. A Price-Jones curve (Fig. 3) demonstrates the erythrocyte diameter. Reticulocytes were 0·9%, leucocytes 7,900/c.mm., of which 5,800 were lymphocytes. Thrombocytes were 74,000/c.mm. The bone marrow was megaloblastic. The ascorbic acid content of the blood was 1·1 mg.%. As a safety measure the child was treated at home. The only treatment consisted of the addition of 200 g. fresh endive daily to the existing diet. After 12 days reticulocytes had increased to 30% (Fig. 4). After 30 days the haemoglobin was 60% and the anaemia had become normocytic. The general condition had improved considerably. Recovery was uneventful; there was no relapse.

In this patient the experimental conditions were ideal, as surrounding and dietary circumstances remained constant, which made it certain that the results were due to treatment.

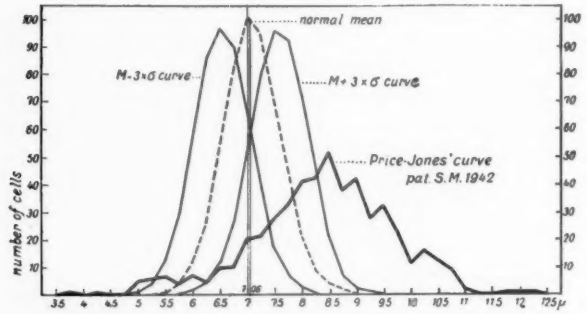

FIG. 3.—Case 2. Price-Jones curve.

Case 3. On February 27, 1949, a normal pregnancy ended after normal delivery with the birth of a child, a boy, weighing 3,200 g. He was the second child. The first was raised on goat's milk with excellent results.

This child was breast fed for the first three months and gained weight satisfactorily. He was then given supplementary feeds of goat's milk in increasing quantities (with water, sugar and flour), till at the age of 5 months he was given goat's milk exclusively. He also received tomato juice from 5 months. During the last three or four months the appetite had gone, the child vomited from time to time, and became increasingly pale. There had been no infections except for a cold in the previous few weeks.

On admission on October 27, 1949, the child was 8 months old, weighed 6,400 g. and was 67 cm. tall. He appeared ill, was dystrophic, listless and severely anaemic. A systolic murmur was heard over the heart, the liver extended one and a half fingerbreadths under the costal margin, the spleen could not be palpated. The temperature was 38·5° C. and remained elevated during the first few days. There were no other abnormalities. Haemoglobin was 22%. Erythrocytes were 800,000/c.mm., with anisocytosis, poikilocytosis, polychromasia; the colour index was 1·25. The Price-Jones curve (Fig. 5) demonstrates the size and the scattering of the erythrocytes. Reticulocytes were 1·6%. Leucocytes were 17,200/c.mm., (myelocytes 2, band forms 2, polymorphs 21, eosinophils 4, lymphocytes 70, monocytes 1, erythroblasts 12). Thrombocytes were 1,008,000/c.mm. The bone marrow was megaloblastic.

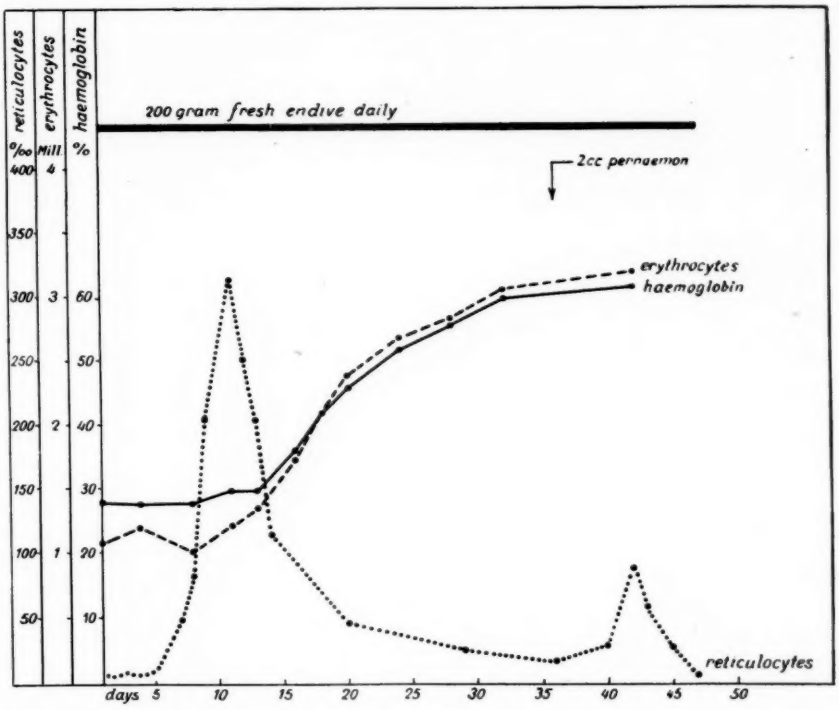

FIG. 4.—Case 2. Reticulocyte crisis and improvement in blood count.

Immediately on admission the child was given a transfusion of 100 ml. whole blood. Haemoglobin was 38% on the next day. The diet consisted of goat's milk, with water, flour and sugar added in suitable quantities; at the same time 100 g. of fresh endive daily was added. After eight days a reticulocyte crisis was noted of 15·6% (Fig. 6). After three weeks haemoglobin was 60% with 3,740,000/c.mm. erythrocytes, the weight increasing in the meantime by 730 g. The general condition had improved remarkably, in spite of an upper respiratory infection. The patient was discharged on December 17, 1949, with a haemoglobin of 75% and 4,350,000 erythrocytes/c.mm.

Three weeks after admission the child was put on an adequate diet: two weeks later it was started on oral lactas ferrosus.

During long-continued feeding with goat's milk exclusively megalocytic hyperchromic anaemia developed, which was treated by adding a daily dose of 100 g. fresh endive to the goat's milk diet, and cleared up with a reticulocyte crisis.

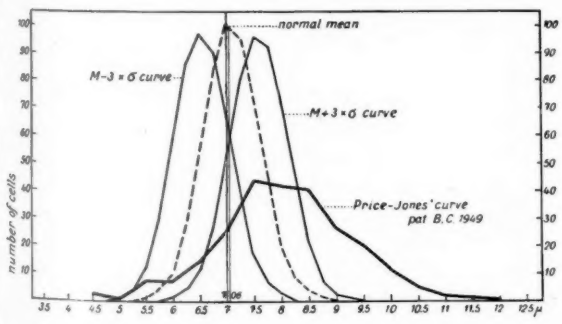

FIG. 5.—Case 3. Price-Jones curve.

Case 4. On January 12, 1950, this child, a boy and the first of healthy parents, was born normally after an uneventful pregnancy, with a birth weight of 2,500 g. He was artificially fed, correctly in quantity and quality, but often refused fruit juice and never took vegetables, Development was normal up to the age of 6 months. After that the patient started to vomit with increasing frequency. Before admission the child was feverish.

On October 9, 1950, the child was admitted to hospital. He was then 10 months old, weighed 6,430 g. and was 67 cm. tall. He looked ill, apathetic and pale; the nutritional condition was adequate, the temperature was 38·3° C. There was infection of the upper respiratory tract. A systolic murmur was heard over

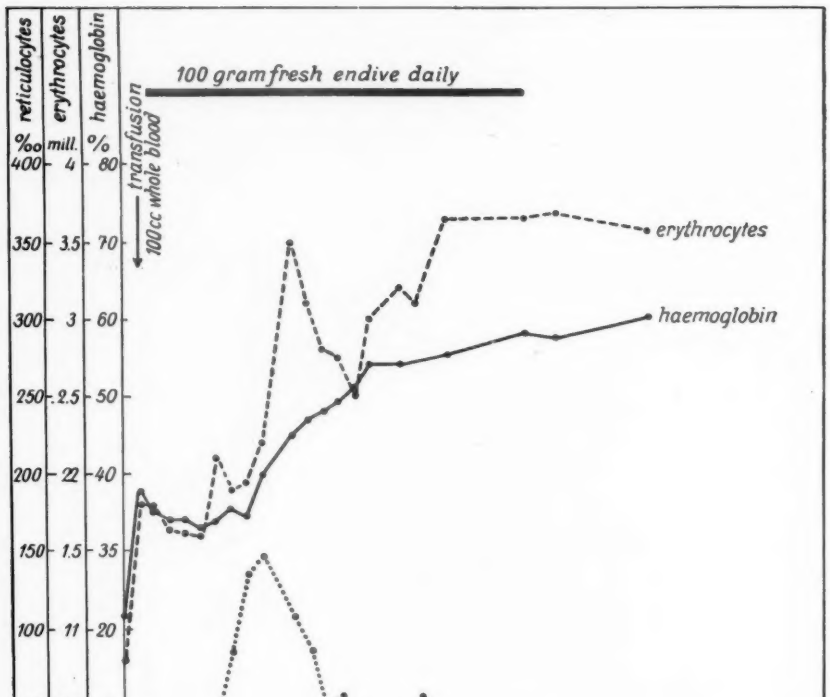

FIG. 6.—Case 3. Reticulocyte crisis and improvement in blood count.

the heart. Breathing was normal. The liver, spleen and lymph nodes were not enlarged. On the left cheek there was a blue spot (2 cm. diameter). Examination of urine, faeces and cerebrospinal fluid was negative.

Haemoglobin was 27%, erythrocytes were 1,220,000/c.mm., with anisocytosis, poikilocytosis, polychromasia. The colour index was 1·16. A Price-Jones curve demonstrates the size and scattering of the red cells (Fig. 7). Reticulocytes were 2%. The E.S.R. was 5 mm. Leucocytes were 6,900/c.mm. (4,623 lymphocytes). A differential count gave band forms 2, polymorphs 26, lymphocytes 67, monocytes 4.

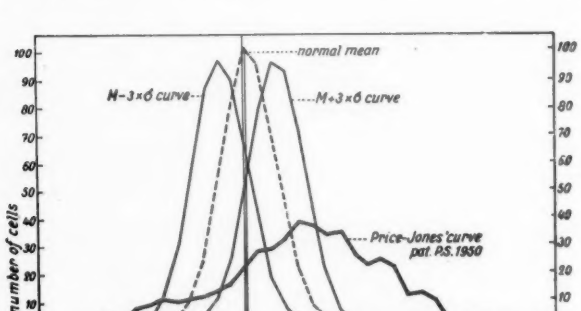

FIG. 7.—Case 4. Price-Jones curve.

Thrombocytes were 12,200/c.mm. The coagulation time was 1 minute and the bleeding time 4 minutes 45 seconds. The bone marrow was megaloblastic.

The diet of the patient was left unchanged; it consisted of milk, 700 ml., water 200 ml., flour 60 g., sugar 20 g., divided over four feeds. Also 1,000 I.U. of vitamin D and 1,000 I.U. of vitamin A were given. To this was added 25 g. fresh minced endive.

After one week of treatment the condition and behaviour changed completely and a reticulocyte crisis occurred (Fig. 8). In this week the child became lively and interested in his surroundings. After 20 days the haemoglobin was 63%, and the number of red cells 3,700,000/c.mm. The weight had increased by 250 g. Endive was then discontinued and the child was put on a diet adequate for his age. The haemoglobin level, from then on, increased only very slowly. Iron preparations had little effect. After 50 days the patient was discharged with a haemoglobin of 77% and 5,250,000 erythrocytes/c.mm.

The experimental conditions in this case were correct. The recovery could be ascribed to the fresh endive added to the original diet.

Discussion

Considering the influence of fresh endive on the condition resulting from a long-continued exclusively milk diet, it is of interest to know the folic acid content of this vegetable. This is, when fresh, 0·62-0·75γ/g. (Fager, Olson, Burris and Elvehjem, 1949). Case 2 received 200 g. fresh endive, which amounts to 124-150 γ folic acid per day, Case 3 received only 62-75 γ daily, Case 4, 15-19 γ daily. This is a few hundred times less than the amount with which a reticulocyte crisis and recovery are usually effected in these patients. It is improbable that differences in folic acid content of this order exist between American and Dutch endive. It is therefore doubtful whether reaction and recovery in our patients, during treatment with fresh vegetables and fruit or fresh endive, is attributable to its content of folic acid alone. It seems probable that another substance is involved. If guinea-pigs

develop scurvy on a diet entirely free of ascorbic acid and are then fed the same diet either with the addition of ascorbic acid or of tomato juice, a similar incongruity is encountered. In order to effect the same degree of recovery more crystalline vitamin C is needed than is contained in the tomato juice in its natural state. In this connexion the work of May, Nelson, Lowe and Salmon (1950) is of interest, as they point out that vitamin C deficiency may also play a role in the development of megalocytic anaemia. The findings in Cases 1 and 2 do not appear to confirm this, as they had received ample vitamin C, but this was only given when the anaemia had already developed. It is after all possible that May's explanation holds good for these patients. If it is indeed possible to cure this anaemia by the combined administration of folic acid and vitamin C, it is still remarkable that these are needed in very small amounts. The vitamin C content of endive is 12 mg.%. The last patient received only 3 mg. vitamin C per day. Thirty-one days after the beginning of treatment, the vitamin C content of the blood was determined, and was 0·2 mg.%. It seems indicated to treat such patients with similarly small doses of crystalline folic acid and vitamin C. But the possibility is by no means excluded that endive contains traces of other substances which aid in accelerating the curative process.

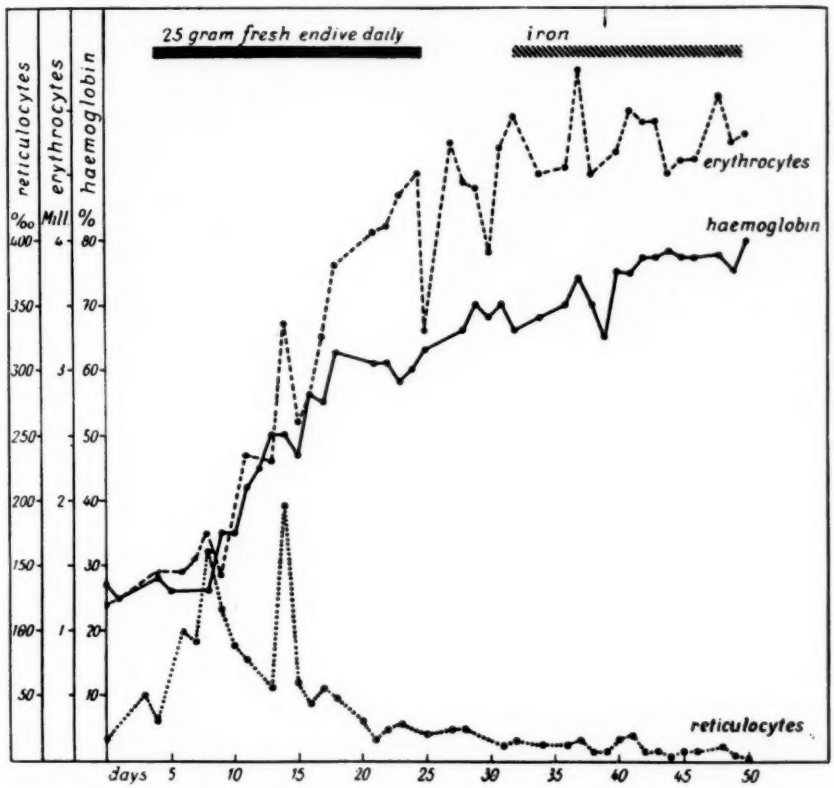

FIG. 8.—Case 4. Reticulocyte crisis and improvement in blood count.

and fresh fruit to the previous diet (1939). The second patient was cured by means of a dosage of 200 g. fresh endive added to the preceding diet, the third received 100 g. endive with his diet and the fourth only got 25 g. fresh endive with the same diet as before.

Fresh endive apparently contains substances which are able to cure megalocytic hyperchromic anaemia. The folic acid content of fresh endive is 62-75 γ per 100 g. and its vitamin C content is 12 mg.%. The last patient received only 15-19 γ folic acid and 3 mg. vitamin C daily. The possibility that other substances contributed to this cure must be considered.

Summary

Four cases of megalocytic hyperchromic deficiency anaemia are described occurring at the end of the first year of life. One of these patients had been fed exclusively on goat's milk; three had had a long-continued diet of cow's milk. All patients promptly and definitely recovered, with a reticulocyte crisis. Treatment varied: the first patient recovered with the addition of fresh vegetables

References

Bachman, A. L. (1936). *Amer. J. Dis. Child.*, **52**, 633.
Faber, H. K. (1928). *Ibid.*, **36**, 1121.
Fager, E. E. C., Olson, O. E., Burris, R. H. and Elvehjem, C. A. (1949). *Food Res.*, **14**, 1.
McPherson, A. Z., Jonsson, U. and Rundles, R. W. (1949). *J. Pediat.*, **34**, 529.
May, C. D., Nelson, E. N., Lowe, C. U. and Salmon, R. J. (1950). *Amer. J. Dis. Child.*, **80**, 191.
Starck, W. von (1909). *Jb. Kinderheilk.*, **69**, 264.
Veeneklaas, G. M. H. (1940). *Ned. T. Geneesk.*, **84**, 3860 and 4517.
—— (1942). *Folia haemat., Lpz.*, **65**, 303.
—— (1943). *Ned. T. Geneesk.*, **87**, 1670.
—— (1947). *Ibid.*, **91**, 316.
Zuelzer, W. W. and Ogden, F. N. (1946). *Amer. J. Dis. Child.*, **71**, 211.

BLOOD FORMATION IN INFANCY

PART II. NORMAL ERYTHROPOIESIS*

BY

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(RECEIVED FOR PUBLICATION AUGUST 23, 1951)

There is general agreement that the fall in haemoglobin after birth is an expression of the increased oxygen saturation of the blood when lung replaces placenta as a source of oxygen. We have sought to express this idea concretely, to show that the changes which occur in the form and number of red cells after birth are due to variations in the erythropoietic activity of the marrow, and finally to infer that this activity is itself governed by the need to maintain the oxygen content of the blood at a constant level.

Material and Methods

The material was the same as has been described in Part I, consisting of 105 samples of venous blood together with 102 bone marrow samples, taken from 25 infants from birth to 3 months.

Our methods have been described in Part I. They were chosen after considering the following probable causes of the divergent results of previous authors in this field. Differences in haemoglobinometry may cause discrepancies, as may differences in methods of sampling. Skin prick samples of blood are apt to give variable results according to the site and depth of puncture, and tend to give higher values than venous samples, this effect being large in the first week of life (Vahlquist, 1941; DeMarsh, Alt and Windle, 1948; Oettinger and Mills, 1949). Consistent and reproducible results are most surely obtained by venous sampling, which was used exclusively in the present study. Differences in delay before clamping the cord may also affect results. Although DeMarsh, Alt and Windle (1941) list authors as far back as 1877 who have investigated the influence of this factor upon the post-natal blood picture, many subsequent studies have ignored it. Early clamping of the cord was the rule in this series. Differences in infants' growth rates, as Washburn (1941) has clearly shown, are the main factor influencing the rate of decrease in red cell level during the first two months of life. In this context it will often be convenient to consider the total mass of circulating haemoglobin or total red cells as well as their concentrations; the method for calculating these has been described in Part I. Reticulocyte levels have been commonly used as a measure of erythropoiesis in infants, although it is well known that during a period of sustained red cell production it is only initially that the reticulocytes are numerous. We have measured erythropoiesis by enumerating the erythroid cells in the bone marrow (see Part I).

Results

Fig. 1 shows the changes in the red cell picture from birth to 3 months. The main trends follow those established by others: after birth the haemoglobin level rises abruptly and then falls until the eighth week, thereafter remaining at a level of 11 to 12 g. The red cell level falls proportionately less steeply, due to the coincident decrease in cell size as measured by the mean cell volume (M.C.V.).

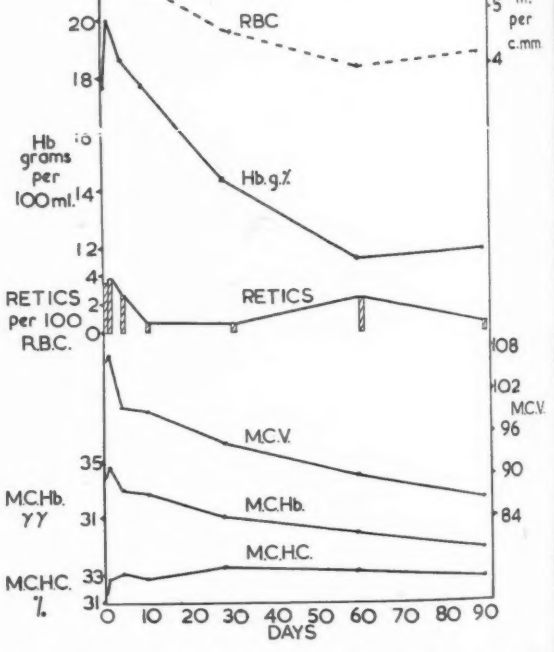

FIG. 1.—Changes in the red blood cells from birth to 3 months.

* Part I was published in the April issue (27, 128).

The mean corpuscular haemoglobin concentration (M.C.H.C.) remains practically constant throughout. In describing these changes in detail it will be convenient to mention at this stage one conclusion to which the results point—that the erythropoietic system of the infant is 'set' to maintain a constant oxygen content in arterial blood, equivalent, under normal conditions of blood oxygenation, to a haemoglobin concentration of 11 to 12 g. per 100 ml. With this principle in mind the first three months of life fall into three phases: (1) the first week of life, when the haemoglobin level remains above the level at birth; (2) from the second to about the eighth week, when the haemoglobin level steadily falls to the level of 11 to 12 g.; (3) from the eighth week onwards, when the haemoglobin level is maintained at 11 to 12 g.

(1) From Birth to 9 Days. Fig. 2 shows the essential facts covering this period. The haemoglobin level rises abruptly after birth, so that on Day 1 (2-24 hours) it is 12% above the cord blood level; thereafter it declines, returning to the level in cord blood by Day 9. The calculated value for the total haemoglobin also appears much higher on Day 1 than at birth, but by Day 4 has already returned to the value at birth, and remains at the same value on Day 9. The red cell count (Fig. 1) shows similar changes. Erythropoiesis diminishes rapidly after birth; at birth the marrow erythroid count (see Part I) is high, 41,000 per c.mm., but by Day 4 this figure has fallen to 7,000, and by Day 9 to 2,800. Reticulocytes, from high levels at 3·5% at birth and 3·9% on Day 1, likewise fall steadily.

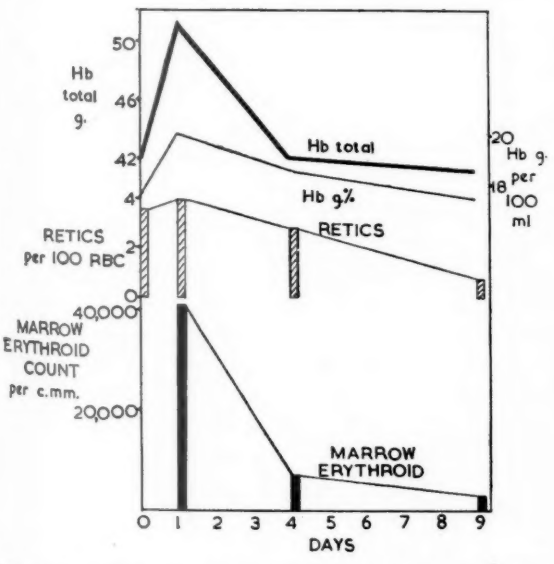

FIG. 2.—Changes in haemoglobin concentration, total haemoglobin, reticulocytes and marrow erythroid count, from birth to 3 months.

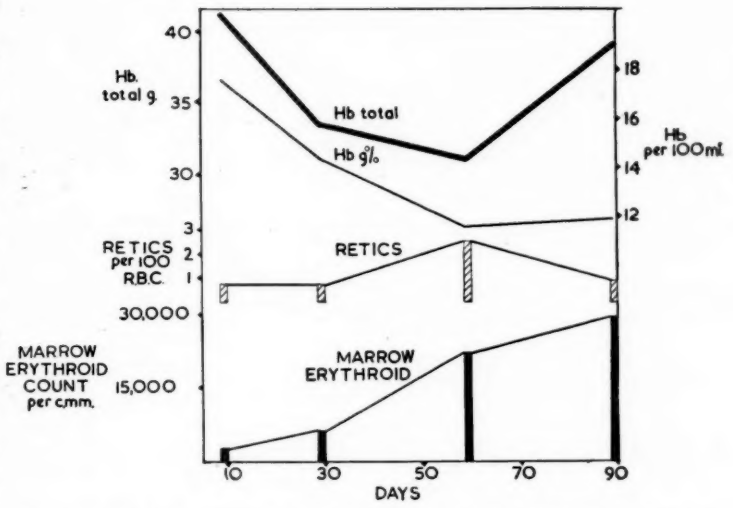

FIG. 3.—Changes in haemoglobin concentration, total haemoglobin, reticulocytes and marrow erythroid count from nine to 89 days.

(2) Days 9 to 59. During this period the haemoglobin level falls (Fig. 3) until by the end of the second month it has reached a level of 11 to 12 g. per 100 ml. The total haemoglobin falls also at first rapidly (Days 9 to 29), then more slowly (Days 29 to 59). Fig. 4 shows the rate of disappearance of total haemoglobin in 14 individual subjects in the phase of rapid fall; the fact that the majority of the lines show much the same slope points to the existence of some single factor which controls the rate of disappearance of haemoglobin. The average rate of disappearance of haemoglobin from Days 9 to 29 is 0·90% per day. The corresponding figure for total red cells is calculated as 0·70% per day. The significance of these figures will be discussed presently. Erythropoiesis is at a low level at the beginning of this period, the marrow erythroid count being 2,800 per c.mm. on Day 9. As the haemoglobin level falls the marrow erythroid count tends to rise, so that by Day 29 when the haemoglobin level has fallen to 14·4 g. the marrow erythroid count has risen to 6,300 per c.mm. As the haemoglobin approaches the level of 11 to 12 g. erythropoiesis rises sharply, so that by Day 59 when the haemoglobin has fallen to 11·4 g. the marrow erythroid count has risen to 22,000, and the reticulocytes to 2·5% from previous values during this period of under 1%.

(3) Days 59 to 89. Throughout this period the high level of erythropoiesis (Fig. 3), as measured by the marrow erythroid count, is sustained

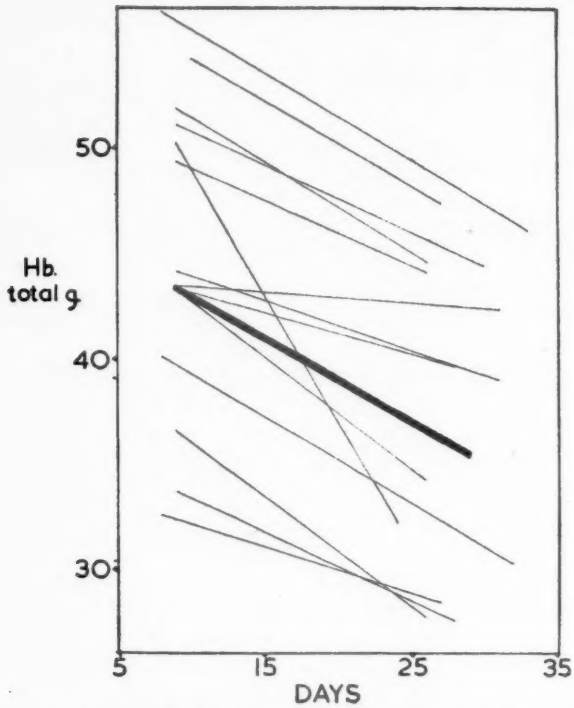

FIG. 4.—Rate of decline of total haemoglobin between Days 8 and 32 in 14 infants. The slope of the majority lies near the mean, shown by the thick line. (The graph with the exceptionally large slope almost certainly resulted from an experimental error.)

(22,000 per c.mm. on Day 59, 30,000 on Day 89). Consequently the total haemoglobin now rises steeply with a gain of 10 g. in 30 days. Nevertheless, as this rate of gain is matched by the rate of body growth, the haemoglobin concentration changes only insignificantly from 11·6 to 11·9 g.%.

Discussion

The facts so far elicited fall into place if we suppose that the erythropoietic tissue is sensitive to variations in the oxygen content of arterial blood, and that it is 'set' to maintain the oxygen content at a level which is constant for a given age. It will be shown that throughout the first 18 months this level corresponds to a concentration of oxyhaemoglobin of about 11 g. per 100 ml., and that a similar level obtains in late foetal life.

Changes in Haemoglobin Level Immediately after Birth. In the foregoing section the general shape of the haemoglobin curve over the first three months has been explained on the assumption that the level of erythropoiesis is determined by the divergence of the haemoglobin from the level of 11 to 12 g. At birth the haemoglobin lies far above this level, hence erythropoiesis soon falls to a very low level and the haemoglobin consequently declines. As the haemoglobin approaches a level of 11 and 12 g. erythropoiesis increases so that the decline in haemoglobin is first slowed and then arrested, erythropoiesis being finally adjusted to maintain the haemoglobin level constant at 11 to 12 g.

Additional factors are responsible for the changes in the red cell picture immediately after birth. Our results (Fig. 2) show that whereas the haemoglobin in cord blood averaged 17·6 g., the haemoglobin at two to 24 hours averaged 20·0 g., that is 12% higher. A difference of the same order was noted in each of three individual subjects where blood samples taken two and a half, three and seven hours after birth could be compared with cord blood. The fact that within a few hours of birth the concentration of haemoglobin is considerably higher than in cord blood is apparent also in the figures given by Vahlquist (1941) and Mollison and Cutbush (1949), although no such difference was found by Waugh, Merchant and Maughan (1940). (In considering the effect it is

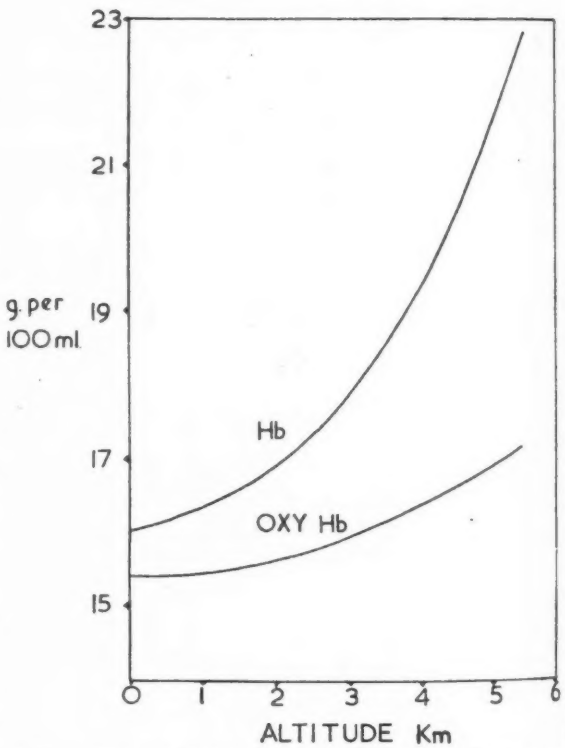

FIG. 5.—Effect of altitude upon haemoglobin and (arterial) oxyhaemoglobin levels, from data collected by Hurtado *et al.* (1945). Note relative constancy of oxyhaemoglobin.

important to confine attention to data relating to venous samples.) None of these authors made any special attempt to clamp the cord early. DeMarsh, Windle and Alt (1942) compared the haematocrit of cord blood with that of venous blood taken one quarter to three hours after birth and found that a rise in haematocrit occurred only when the cord was clamped late. When it was clamped early there was no such rise.

If a transfer of placental blood is the cause of the immediate post-natal rise in haemoglobin, a gain by the infant of at least 40 ml. of placental blood would be necessary to account for the rise observed in our series. Although the cord was clamped as early as conveniently possible, 10-15 seconds usually elapsed after the birth of the infant, and it is conceivable that a transfer of as much as 40 ml. of blood could take place in this period, since Haselhorst and Allmeling (1930) showed that the average amount of blood in the placental circuit was 104 ml. and that 51% of this was transferred to the infant in the first minute after birth. Possibly also some placental blood transfer may take place in the terminal phases of delivery.

However, we do not regard it as yet settled that placental blood transfer is the sole factor causing the post-natal rise in haemoglobin. It seems not impossible that other factors may play some part, such as, for instance, a temporary redistribution of body fluids causing haemoconcentration. We are making a closer study of the changes in the blood picture immediately after birth, which will be the subject of a further communication. Meanwhile we regard with reserve the values we have calculated for total haemoglobin and red cells at birth and on Day 1.

From Day 4 to Day 9 the picture is clearer. Fig. 2 shows that the total haemoglobin remains unchanged over this period, so that red cell destruction is now balanced by formation. Although the erythroid cells in the marrow fall to a low level during the first nine days after birth, those cells present in the marrow at birth must continue to mature, so that it is only when the momentum of foetal erythropoiesis has spent itself, some time during the second week, that the total haemoglobin begins to fall.

Constancy of Oxyhaemoglobin Level in Foetus and Infant. Although it is generally accepted that the decline in haemoglobin level after birth is related to the different degree of oxygen saturation of blood in intra-uterine and extra-uterine life, it is useful to put this idea into concrete terms. We have shown that once the haemoglobin concentration has fallen to 11 to 12 g. erythropoiesis is adjusted to maintain this level. Our own studies have followed this process only as far as the third month, but there is general agreement from the work of others that from the third month to 18 months the haemoglobin remains substantially unchanged at about 11 to 12 g. per 100 ml. (Mackay, 1933; Josephs, 1936; Magnusson, 1935; Mugrage and Andresen, 1936; Guest, Brown and Wing, 1938; Vahlquist, 1941; Selander, 1944; Findlay, 1946; Horan, 1950). Only Merritt and Davidson (1934) and Faxen (1937) give a rather higher figure of 12 to 13 g. Since arterial blood is 95% saturated with oxygen we can conclude that the oxyhaemoglobin level from the third month to 18 months is maintained at about 11 g. per 100 ml.

In comparing this with the level in intra-uterine life one finds that the few available measurements of the oxygen saturation of foetal umbilical vein blood vary widely, but the majority lie between 45% and 80%, with an average of about 65% saturation. (The matter is reviewed by Barcroft (1946) and by Smith (1945): the former also found that in the sheep foetus at term the oxygen saturation of umbilical vein blood is 65%.) If we take the figure of 65% saturation and apply it to the average cord blood haemoglobin in our series, 17·6 g. per 100 ml., we arrive at a value of 11·4 g. per 100 ml. for the concentration of oxyhaemoglobin in the arterial blood of the foetus at the end of gestation. In view of the doubt as to the data from which this figure is derived, it is not of great significance that the calculated oxyhaemoglobin level in the arterial blood of the foetus corresponds so closely to that found in the infant after post-natal adjustment of the haemoglobin level has had time to take place. Nor have we taken into account the fact that in the foetus arterial blood is partly mixed with venous blood and so is less oxygenated than umbilical vein blood. The figures nevertheless illustrate the general principle that under widely different conditions of oxygenation the haemoglobin level is adjusted to give an oxyhaemoglobin level which changes relatively little.

That this principle is of wide application can be illustrated from two further sources. Barcroft (1946), working with the sheep foetus, has shown that owing to differences in the rates of growth of placenta and foetus, the oxygen saturation of umbilical vein blood fluctuates throughout gestation: nevertheless the oxygen content of umbilical vein blood is maintained at a roughly constant level, since when its oxygen saturation is low, this is balanced by an increased oxygen capacity. This is equivalent to saying that the haemoglobin level varies in such a way that the oxyhaemoglobin level is maintained constant.

Fig. 5 is based on figures collected by Hurtado,

Merino and Delgado (1945) for the haemoglobin level and oxygen saturation of dwellers at high altitude. It shows that as altitude and the resulting anoxia increase, so the haemoglobin level rises steeply, while the oxyhaemoglobin is maintained at a level differing only slightly from that obtaining at sea level.

Erythropoietic Response to Variations in Oxyhaemoglobin Level. Within three hours of birth the infant achieves an adult level of 95% arterial oxygen saturation (Smith, 1946), so that, assuming that erythropoiesis is dependent upon the level of oxyhaemoglobin, when dealing with normal subjects we can conveniently use the haemoglobin level as a measure of the stimulus to erythropoiesis. The changes shown by the marrow erythroid count—its rapid fall after birth, its persistence at a low level until the haemoglobin begins to approach 11 to 12 g. per 100 ml., and its gradual rise at this stage—have already been shown to accord with the simple principle that erythropoiesis depends upon the stimulus of a haemoglobin level lying near to, or below, the optimal level. Fig. 6 shows that erythropoiesis is in general active only when the haemoglobin level falls below 15 g., and that there is then a fairly close correlation between the amount of erythropoietic activity, as measured by the marrow erythroid count and the haemoglobin level.

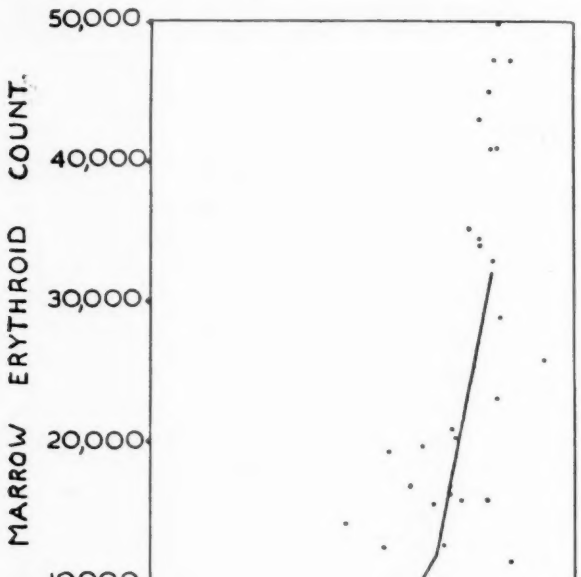

FIG. 6.—Relationship between erythropoietic activity of marrow and haemoglobin level of blood in normal infants aged from 8 to 84 days. The line roughly indicates the trend, which shows that erythropoiesis is at a low level when the haemoglobin lies above 15 g.%, and rises steeply as the haemoglobin falls below this level.

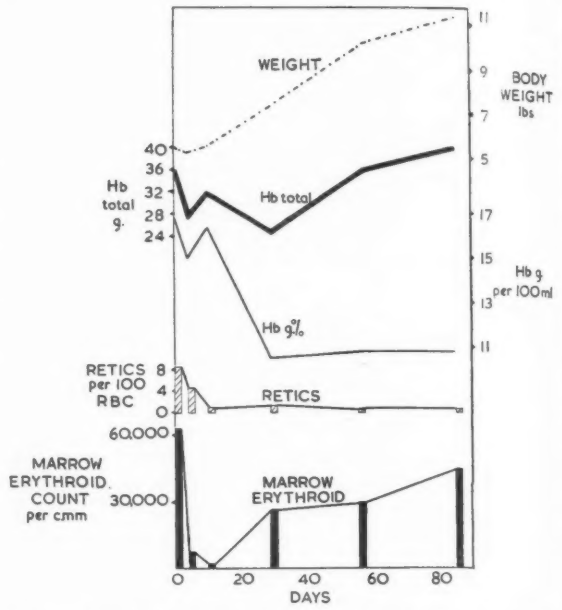

FIG. 7.—Course of erythropoiesis in an infant with rapid growth. Compare with average infant in Fig. 3.

The principle that erythropoiesis depends upon the stimulus of an optimal or sub-optimal level of oxyhaemoglobin is further illustrated by two individual subjects. The first (Fig. 7) shows the blood and marrow changes in an infant with a rapid weight gain, the low birth weight (5½ lb.) being doubled in 12 weeks. Although the rate of decline of the total haemoglobin is normal, 0·90% per day, the rapid weight gain brings about an abnormally rapid decline in haemoglobin concentration, so that at Day 29 this has already fallen to 10·5 g. per 100 ml. At this stage erythropoietic activity increases, as shown by the rise in marrow erythroid count, the total haemoglobin starts to rise, while the haemoglobin concentration remains at 11 to 12 g. These are the changes seen normally, except that in this case they occur a month earlier than usual on account of the earlier decline of haemoglobin to the critical level of 11 g. per 100 ml.

By contrast Fig. 8 shows the blood and marrow changes in an infant with congenital heart disease causing severe cyanosis, that is, a low oxygen saturation. There is an absence of the fall in erythropoiesis normally seen after birth, the marrow erythroid count remaining constantly at 8,000

to 10,000 per c.mm., and the reticulocytes tending to remain above 2%. In this case instead of the haemoglobin showing the usual fall over the first two months, it rises to a level of 15·6 g. per 100 ml.

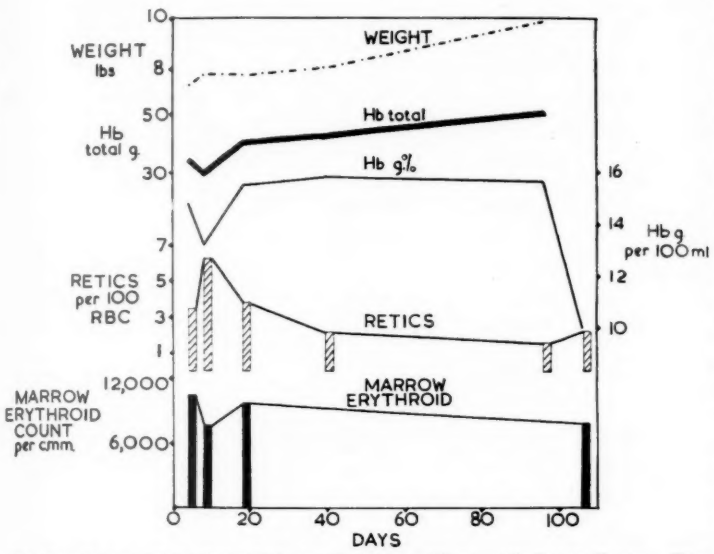

FIG. 8.—Course of erythropoiesis in an infant with cyanotic heart disease. The reticulocyte and marrow erythroid counts show no post-natal fall, and the haemoglobin level is maintained at about 16 g.% until terminal circulatory failure at 106th day.

at 19 days and remains about this level until death from heart failure at 15 weeks.

The Size of the Red Cell. Our figures (Fig. 1), in common with those of others, show that at birth the mean cell volume is high (M.C.V.=107 c.μ), thereafter decreasing until at three months it has reached adult values (87 c.μ). It is known (Wintrobe, 1946) that there is a progressive decrease in red cell size throughout foetal life, whence it follows that the high M.C.V. present at birth is due to a proportion of the red cell population being made up of large cells laid down some time before the end of gestation. Thus if we suppose that the average life of the red cell in the foetus is 120 days as in the adult, some of the red cells at birth will have been laid down at a foetal age of 160 days when, according to Wintrobe, the M.C.V. is 130 c.μ. Those red cells coming to the end of their span would thus have a larger size than the average, and in this way a progressive decrease in M.C.V. would occur, as has been suggested by Mollison (1948).

It is interesting to note that anoxaemia is capable of partially reversing the normal disappearance of the macrocytosis of foetal life, for the red cells both of dwellers at high altitudes and of children with cyanotic heart disease show an increased M.C.V. (Hurtado *et al.*, 1945; Prader, Rossi and Holländer, 1950).

The Rate of Red Cell Destruction. In the older literature it was taken for granted that the post-natal fall in haemoglobin and red cells was due to rapid haemolysis: for instance, Josephs, reviewing the subject in 1936, concluded that this factor was of comparable importance to the reduced level of erythropoiesis. Although we have made no direct measurements of the rate of red cell destruction, it is possible from our data to show that variations in erythropoiesis alone are adequate to account for changes in haemoglobin and red cell levels, assuming that in infants the life span of a red cell is about the same as that accepted for adults, evidence for which will be discussed.

Over the first nine days of life we have shown (Fig. 2) that there is no fall in total haemoglobin. Other studies which have employed venous samples have also shown that compared with cord blood, the haemoglobin concentration at the tenth to the fourteenth day is either rather higher (Guest *et al.*, 1938; Vahlquist, 1941) or only slightly lower (Waugh, Merchant and Maughan, 1940). This significant fact has been obscured when capillary samples have been used, since the haemoglobin value of capillary blood, which at birth is markedly higher than that of venous blood, progressively approaches the latter during the first one or two weeks (Vahlquist, 1941; Oettinger and Mills, 1949). We conclude that there is nothing pointing to unusually rapid blood destruction during the first nine days after birth.

The succeeding period from nine to 29 days corresponds to the period of maximum rate of fall in haemoglobin (Figs. 3 and 4). During this period the rate of disappearance of total haemoglobin is 0·90% per day, and of the total red cells 0·70% per day. (The difference between the two is due to the fact that the red cells which disappear are larger than normal and have a higher haemoglobin content.) The figure for the decline of red cells differs by only 16% from the rate of 0·83% per day which would be anticipated if no new red cells were being added, and the existing red cells had a span of 120 days. This difference would be accounted for if red cells were being formed at the rate of one to every six cells destroyed. Such a low rate of erythropoiesis is in keeping with the low marrow erythroid count obtaining throughout

this period (Fig. 3). Thus during the first four weeks of life the changes in red cells and haemoglobin can be simply accounted for on the basis of a normal rate of red cell breakdown.

We must now consider other evidence bearing on this conclusion. The rate of disappearance of distinguishable cells is the most direct method of investigating the matter, and easily shows up the fate of different types of red cells in infants with haemolytic disease, Rh-positive cells disappearing usually within 10 days, Rh-negative cells surviving about 90 days (Mollison, 1943); the latter figure agrees well with the survival of red cells transfused into adults (Wintrobe, 1946). Hedenstedt and Vahlquist (1948) have measured the survival of elliptocytes transfused into newborn infants and find this to be the same as in older children. Such experiments indicate that transfused adult red cells are destroyed by young infants at the normal rate. The question remains whether the newborn infant's own red cells are destroyed more rapidly. Mollison (1951) compared the survival of placental and adult blood transfused simultaneously into anaemic infants and concluded that the mean cell life of the 'placental' red cells was a little shorter than that of the 'adult' red cells. However, the difference was small and, without the observations on the control population of adult red cells, would have been difficult to demonstrate. (Earlier, the same author had reported a distinctly greater rate of fall in the concentration of placental red cells during the first 10 days after transfusion (Mollison, 1948); however this was probably due to the initial values having been falsely high as a result of using skin-prick samples (Mollison, 1951). An explanation of this effect would probably be forthcoming if we knew how cells of different ages were distributed amongst the cell population at birth. If, for example, we supposed that about 110 days before birth erythropoiesis is particularly active, then an infant at birth would possess a large complement of cells nearing the end of their span of 120 days, so that an undue proportion of red cells would disappear during the first 10 days after birth. An explanation along some such lines may account for Mollison's (1951) finding.

Less direct methods of investigating the matter have also been employed. Using bile pigment excretion as a measure of red cell breakdown, Josephs (1934) and more recently Künzer (1951) reached the conclusion that excessive red cell breakdown is a factor in the decline of haemoglobin after birth: however, the questionable assumptions implicit in the method must render this conclusion open to doubt. Finally, Vahlquist (1941) from an elaborate study of serum iron in infancy, has provided evidence against the view that there is increased haemolysis after birth.

The fact that if the cord is tied late the chance of an infant developing jaundice is increased (Book, 1935) has been quoted as proof that neonatal jaundice is at least partly haematogenous (Smith, 1946). Since, however, the infant whose cord is tied late receives an addition of about 100 ml. of blood to its existing blood volume of about 300 ml., thereby increasing its total red cells by one third, the normal breakdown of red cells will also increase by one third. Such an increase in the amount of bilirubin liberated would, in the presence of the low excretory capacity of the newborn infant's liver (Mollison and Cutbush, 1949; Yudkin, Gellis and Lappen, 1949), be doubtless enough to account for an increased incidence of jaundice. If this factor is kept in mind the known facts about neonatal jaundice seem to be adequately accounted for on the basis of hepatic immaturity alone.

Thus from a consideration of our own results, together with those of others mentioned, we conclude that there is no important increase in the rate of red cell breakdown in the neonatal period. The effect of plethora in adults is, we know from the recent study of Birkhill, Maloney and Levenson (1951), to cause a virtual cessation of erythropoiesis until the normal blood level has been restored, while red cell breakdown continues at a normal rate. A precisely similar picture emerges when the plethora of the newborn infant is studied.

Summary

The course of erythropoiesis in a series of infants from birth to 3 months has been defined, using the marrow erythroid count as a measure of erythropoiesis.

The factors responsible for the changing red cell picture after birth are two, changes in erythropoietic activity and the effect of body growth. There is no evidence that increased haemolysis is a significant factor.

Erythropoietic activity is governed principally by the arterial oxyhaemoglobin level. From the age of 2 months to 18 months the oxyhaemoglobin is maintained constant at about 11 g. per 100 ml.

In the foetus it is probable that erythropoiesis is also adjusted to maintain a similar level of about 11 g. of oxyhaemoglobin per 100 ml.

References

Barcroft, J. (1946). 'Researches on Pre-natal Life'. Oxford.
Birkhill, F. R., Maloney, M. A. and Levenson, S. M. (1951). *Blood*, **6**, 1021.
Book, N. (1935). *Canad. med. Ass. J.*, **33**, 269.
DeMarsh, Q. B., Alt, H. L. and Windle, W. F. (1941). *J. Amer. med. Ass.*, **116**, 2568.
——, —— —— (1948). *Amer. J. Dis. Child.*, **75**, 860.
——, Windle, W. F. and Alt, H. L. (1942). *Ibid.*, **63**, 1123.
Faxen, N. (1937). *Acta paediatr., Uppsala*, Suppl. 1.

Findlay, L. (1946). *Archives of Disease in Childhood*, **21**, 195.
Guest, G. M., Brown, E. W. and Wing, M. (1938). *Amer. J. Dis. Child.*, **56**, 529.
Haselhorst, G. and Allmeling, A. (1930). *Ibid.*, **98**, 103.
Hedenstedt, S. and Vahlquist, B. (1948). *Acta paediatr., Uppsala*, 35, 355.
Horan, M. (1950). *Archives of Disease in Childhood*, **25**, 110.
Hurtado, A., Merino, C. and Delgado, E. (1945). *Arch. intern. Med.*, **75**, 284.
Josephs, H. W. (1934). *Bull. Johns Hopk. Hosp.*, **55**, 335.
—— (1936). *Medicine, Baltimore*, **15**, 307.
Künzer, W. (1951). 'Über den Blutfarbstoffwechsel gesunder Säuglinge und Kinder.' *Bibl. paediat., Basel*, No. 51.
Mackay, H. M. M. (1933). *Archives of Disease in Childhood*, **8**, 251.
Magnusson, J. H. (1935). *Acta paediatr., Uppsala*, **18**, Suppl. 1.
Merritt, K. K. and Davidson, L. T. (1934). *Amer. J. Dis. Child.*, 47, 261.
Mollison, P. L. (1943). *Archives of Disease in Childhood*, **18**, 161.
—— (1948). *Lancet*, **1**, 513.
—— (1951). 'Blood Transfusion in Clinical Medicine.' Oxford.
Mollison, P. L. and Cutbush, L. M. (1949). *Archives of Disease in Childhood*, **24**, 7.
Mugrage, E. R. and Andresen, M. I. (1936). *Amer. J. Dis. Child.*, **51**, 775.
Oettinger, L., and Mills, W. B. (1949). *J. Pediat.*, **35**, 362.
Prader, A., Rossi, E., and Holländer, L. (1950). 6th International Congress of Pediatrics, Zürich.
Selander, P. (1944). *Acta paediatr., Uppsala*, **32**, 38.
Smith, C. A. (1945). 'Physiology of the Newborn Infant.' Springfield, Ill.
Vahlquist, B. C. (1941). *Acta paediatr., Uppsala*, **28**, Suppl. 5, Chaps. 9, 10.
Washburn, A. H. (1941). *Amer. J. Dis. Child.*, **62**, 530.
Waugh, T. R., Merchant, F. T. and Maughan, G. B. (1940). *Amer. J. med. Sci.*, **199**, 9.
Wintrobe, M. M. (1946). 'Clinical Hematology,' 2nd ed. London.
Yudkin, S., Gellis, S. S. and Lappen, F. (1949). *Archives of Disease in Childhood*, **24**, 12.

HAEMATOLOGICAL DATA

TABLE I

MEAN VALUES FOR RED CELLS IN VENOUS BLOOD AND FOR ERYTHROID CELLS IN MARROW IN NORMAL INFANTS FROM BIRTH TO 3 MONTHS

Age mean	Birth	Day 1	Day 4	Day 9	Day 29	Day 59	Day 89
Age limits	Cord blood	2–24 hours	3–5 days	8–10 days	26–33 days	55–62 days	82–99 days
Number of cases	12	10	24	22	19	7	11
Haemoglobin (g. per 100 ml.)	17·6	20·0	18·6	17·6	14·4	11·6	11·9
Haemoglobin (total g.)	42·2	51·4	41·9	41·4	33·7	31·1	39·2
Haematocrit	56	63	57	50	44	35	37
R.B.C. (m. per c.mm.)	5·25	5·81	5·67	5·41	4·61	3·91	4·22
R.B.C. (total × 10-9)	1,276	1,502	1,296	1,270	1,093	1,045	1,403
M.C.Hb. ($\gamma\gamma$)	33·7	34·5	32·9	32·7	31·2	29·9	28·7
M.C.V. (c.μ)	107	108	99·3	99·2	94·3	90·0	86·8
M.C.H.C. (%)	31·8	32·6	33·0	32·8	33·5	33·2	32·8
Reticulocytes (per 100 R.B.C.)	3·5	3·9	2·75	0·79	0·76	2·5	0·88
Marrow erythroid count per c.mm.	—	40,632	6,995	2,813	6,316	22,300	29,500

ACUTE IDIOPATHIC HAEMOLYTIC ANAEMIA

BY

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Referring to the disease as new and hitherto unreported, in 1925 Lederer recorded three cases of acute haemolytic anaemia of probably infectious origin. In 1930 he described three additional cases of sudden onset with elevation of temperature, leucocytosis and severe anaemia resembling pernicious anaemia, all of which symptoms promptly and rapidly disappeared following a single transfusion. No mention was made of isohaemolysins or auto-agglutinins in the sera of these patients, the previous work of Chauffard, Troisier and Vincent (1908) and of Widal, Abrami and Brulé (1907) having, apparently, been overlooked.

In view of these earlier descriptions, it seems that the eponym 'Lederer's anaemia' is unwarranted, and that this disease, which responds dramatically to a single transfusion, merely represents one form of acute idiopathic haemolytic anaemia.

Diagnostic Criteria

The features of the disease as defined by Lederer may be expanded: (1) the onset may be acute and fulminating with haemoglobinuria, or subacute, with a history of one to three months of gradually increasing fatigue and weakness accompanied by anaemia and fever (Dameshek and Schwartz, 1940); (2) examination of the blood may show spherocytosis and increased red cell fragility; (3) auto-agglutinins, sometimes present in the serum, may cause difficulty in blood grouping; (4) transfused normal cells are eliminated from the circulation at an accelerated rate (Loutit and Mollison, 1946); (5) recovery, at times spontaneous, may follow transfusions, either single or multiple; (6) response to splenectomy is variable; (7) the history and examination disclose no obvious cause such as bacteria, chemicals, drugs and neoplasms for the haemolytic process; (8) the previous health and family history is devoid of any similar illness.

With intravenous transfusions alone four of the following five patients recovered, while one in whom haemolysis continued died despite splenectomy.

Case Reports

Case 1. Marilyn B., aged 18 months, was admitted to The Hospital for Sick Children, Great Ormond Street, on January 4, 1951, under the care of Dr. W. G. Wyllie. There was a history of loss of appetite for 14 days and fever, with cold, cough and conjunctivitis for 10 days. Two days before admission the cough became more severe, there was a shivering attack and the child vomited once. The following day a second shivering attack occurred accompanied by vomiting, and port wine-coloured urine was passed. Jaundice and pallor were noticed on the day of admission. There was no abdominal pain; the bowels were opened daily. A history of contact with substances known to cause haemolytic anaemia was not obtained.

The patient was an only child. Her father gave a history suggestive of a recent attack of virus pneumonia. Her mother had suffered from a cold 12 days previously. On admission the child was drowsy, very pale, and moderately jaundiced. There was no pyrexia. A purulent nasal discharge was noted and the right tympanic membrane was pink. A systolic murmur was audible at the apex of the heart. No abnormal signs were elicited on examination of the lungs. The liver was palpable half an inch below the costal margin; the spleen was not felt. The napkin was pink.

A spectroscopical examination of the urine performed by Dr. W. W. Payne revealed the presence of methaemoglobin and methaemalbumin. The blood plasma contained methaemalbumin.

The haematological findings were as follows: B.S.R. 90 mm.; blood urea, 74 mg.%; Hb. 36% (Sahli) (5·1 g.%); R.B.C., 1·47 m. per c.mm.; leucocytes, 19,100 (P. 81%, L. 19%); The platelets were agglutinated and uncountable one day after admission; there were 190,720 per c.mm. four days later. Reticulocytes, 4·6%. Anisocytosis, anisochromia and apparent spherocytosis of red cells were reported. No malarial parasites were seen. The direct Coombs, Mourant and Race test was positive on the second, fifth, eighth, 13th, 15th, 19th and 25th days after admission. The blood group of the patient was AII R, mother, OIV R, and father, AII R. Red cell fragility five days after admission: haemolysis began at 0·51% saline concentration and was complete at 0·33%; 13 days after admission, haemolysis began at 0·45% and was complete at 0·36%. The serum Wassermann reaction of the patient and both parents was negative.

The chest radiograph was clear six days after admission.

The father's serum contained no cold agglutinins and a radiograph of his chest was clear. The latter was performed 24 days after the onset, and seven days after recovery from his respiratory illness.

For the following report on this patient's serum and also that of Case 2, I am indebted to Dr. I. A. B. Cathie:

'Owing to auto-agglutination there was some difficulty in determining the patient's blood group, which was eventually established as AII R. The patient's serum contained an antibody which agglutinated the cells of seven AII R donors and nine group OIV R donors. The patient's own cells were also agglutinated. Agglutination was seen only when the cells were suspended in 30% bovine albumin, and in the presence of saline as a diluent no agglutination occurred. As auto-agglutination took place in venous blood withdrawn into a syringe, the above investigations were performed and read at 37° C.'

The mild otitis media was treated with penicillin. AII R blood, 200 ml., was given by syringe, followed by a drip transfusion of 140 ml. In spite of the use of a large Bateman needle, considerable pressure was required to introduce the blood, owing to an obstruction which was thought not to be due to venospasm; it was not relieved by warming the limb, nor by the intravenous injection of 0·5 ml. of nikethamide.

During the transfusion the appearance of irregular-shaped red areas in the skin of the leg proximal to the transfusion site was noted. These disappeared after about four hours, leaving no trace of bruising. Intravascular agglutination of the transfused red cells was considered to be a probable explanation for this phenomenon.

The spleen was enlarged two fingerbreadths below the costal margin after the transfusion, and it remained palpable for 24 hours.

The following day the patient was still pale and jaundiced, the haemoglobin was 44% (6·2 g.%) and the red cell count 2·15 m. per c.mm. The urine contained haemoglobin, and the stools were orange brown. A second transfusion of 400 ml. of blood, from which the plasma had been removed, was given without difficulty or repetition of the previously described phenomenon. Iron therapy was begun.

Four days after admission the haemoglobin had risen to 62% (8·7 g.%), and the reticulocytes were 8·4%. Thereafter, there was a rapid increase in the haemoglobin level, and no further haemoglobinuria.

The patient was last seen on February 19, 1951, six weeks after the onset of the disease. The haemoglobin was 98%, and the Coombs test had become negative.

Case 2. Valerie G., aged 5 years 3 months, was admitted to The Hospital for Sick Children, Great Ormond Street, on January 29, 1951, under the care of Dr. W. G. Wyllie.

One month before admission there was a three-day feverish illness with coryza. Except for two transient, unexplained pyrexial episodes, the patient was then well until the occurrence of a shivering attack two days before admission. This symptom was repeated and was followed on both occasions by the passage of dark red urine. Her mother had suffered from an influenza-like illness for three days; otherwise, the family history revealed no points of importance.

On admission to hospital the child was pale and slightly jaundiced. She had coryza but no cough or fever. The tonsils were enlarged but not injected; the tonsillar glands were palpable. A systolic murmur was present at the apex of the heart. There were râles at the base of the right lung. No enlargement of the liver or spleen was detected.

The urine was a port wine colour and contained a large amount of haemoglobin, methaemoglobin and a moderate excess of urobilin.

The haemoglobin was 59% (8·2 g.%); the red cells, 2·55 m. per c.mm. The percentage of reticulocytes was 1·7; the platelets numbered 137,700 per c.mm. There were 16,000 white cells, of which 76% were neutrophils and 21% lymphocytes. The direct Coombs, Mourant and Race test was positive on the first and seventh day after admission. The red cell fragility began at 0·48% saline concentration and was complete at 0·33%. No lesion was detected in the chest radiograph. Dr. I. A. B. Cathie reported on the patient's serum:

'Group OIV R. The serum contained an antibody which caused agglutination of the red cells of 19 donors of similar group. The reaction occurred when the donor cells were suspended in both 30% bovine albumin and saline. With all the bloods in both diluents agglutination was strong at 37° C., weak at room temperature and negative at 4° C. The patient's serum also caused similar agglutination of her own washed and resuspended cells. The titre of the antibody was not ascertained.'

Treatment included a transfusion of 300 ml. Group OIV R blood, from which the plasma had been removed, iron, and a course of penicillin.

The haemoglobin value rose to 82%, the red cell count to 3·5 m. per c.mm., and the reticulocytes were 1·4% two days following the transfusion. There was no further haemoglobinuria. The patient made an uneventful recovery. She was discharged on February 8, and three weeks later the haemoglobin was 91% (12·7 g.%), the reticulocytes 2·4% and the white cell count 10,000 per c.mm. The Coombs test was positive on this date but negative on March 19, when the patient was last reviewed and found to be healthy.

Case 3. Shirley B., aged 9 years, was admitted to St. Charles' Hospital, London, on February 14, 1950, under the care of Dr. W. G. Wyllie.

For four days before admission there was a poor appetite, the child was pale and listless, the urine was dark, and she had vomited several times each day. No relevant points were disclosed in the previous health and family history.

On admission the temperature was 101·4° F., the pulse 128, and the respirations 24. The patient was a very pale, quiet girl who looked extremely ill. She was not jaundiced. The tonsils were enlarged but not injected; a few cervical glands were palpable. The

heart sounds were accentuated, but no murmur was audible. The lungs were normal. The liver and spleen were not enlarged.

A blood count showed: Hb. 18%; red cells, 1·1 m. per c.mm.; leucocytes, 25,000 (neutrophils 62%, myelocytes 3%, promyelocytes 1%, lymphocytes 26%, monocytes 1·5%). Nucleated red cells numbered 6·5 per 100 white cells; platelets, 250,000.

A red cell fragility test showed haemolysis of 20% of cells at a saline concentration of 0·7%, and 90% at 0·4% saline. As the cells tended to agglutinate spontaneously in saline, little significance could be attached to this result. The test was repeated three weeks later and the result was within normal limits.

Radiographic examination of the chest was normal.

Three days after a transfusion of three pints of blood, a blood count showed: Hb. 82%; leucocytes, 11,000. Slight anisocytosis and polychromasia were reported. The direct and indirect Coombs tests were negative. Total serum proteins were 6·2% (serum albumin, 4·7% and globulin, 1·5%). The serum bilirubin was 1·5 mg.%.

A bone marrow biopsy on February 22, revealed a normoblastic hyperplasia. The picture was characteristic of a post-haemorrhagic or acute haemolytic anaemia followed by a brisk marrow response. There was no evidence of leukaemia (Dr. H. I. Winner).

No cold agglutinins were detected in the serum.

Following the initial transfusion there was no further acute haemolysis, and the temperature became normal five days after admission. When last reviewed, two months after the onset of the illness, the patient was well.

Case 4. Linda P., aged 1 year 10 months, was admitted to The Hospital for Sick Children, Great Ormond Street, on March 5, 1946, under the care of Dr. Donald Paterson.

The patient was well until two days before admission. She then developed abdominal pain associated with constipation, vomited once, and passed dark urine.

On examination she was a pale, slightly jaundiced, drowsy child. Her temperature was 100° F., pulse 140 and respirations 50. No abnormality was elicited in the heart or lungs. The liver and spleen were both just palpable.

A blood count performed on admission showed: Hb. 20%; red cells, 1,410,000; leucocytes, 24,000 (neutrophils 34%, stabs 26%, lymphocytes 34%, monocytes 2%); reticulocytes, less than 1%. Red cell fragility began at 0·48% saline concentration, and was complete at 0·3%. There was no auto-agglutination in the cold or at 37° C. The blood culture was sterile. The serum Wassermann reaction and Kahn test were negative. Serum bilirubin was 2·3 mg.%; the direct Van den Bergh reaction was negative.

Sternal marrow biopsy revealed a marked normoblastic and pro-erythroblastic reaction (Dr. I. A. B. Cathie).

Radiographic examination of the chest was normal.

On April 4, Dr. R. R. Race reported on the patient's blood: 'The cells are autosensitized to rabbit anti-human-serum serum. The group is OIV R'.

The mother's blood was Rh. positive, and no atypical antibodies were present in her serum.

Two blood transfusions resulted in only temporary improvement, and three weeks after admission splenectomy was performed by Mr. Charles Donald. No spleniculi were seen.

Two days after the operation there was a sudden collapse with marked anaemia and jaundice. Repeated transfusions were given, but the haemolytic process persisted. The patient died on April 28, one month after splenectomy.

My thanks are due to Dr. Martin Bodian for his report on the surgical pathology and post-mortem findings:

'The spleen weighed 112 g. with considerable congestion of pulp and reduction of lymphoid tissue. There was no erythropoiesis or evidence of reticulosis. A liver biopsy showed a normal appearance apart from moderate extramedullary erythropoiesis in portal areas. Post-mortem the body weighed 25 lb. Pallor of integument and mucous membranes was observed, also slight jaundice, and cerebral and pulmonary oedema. The liver was enlarged (860 g., normal, 380 g.). There were considerable numbers of iron-containing macrophages in the sinusoids, and erythropoiesis in portal areas and in the sinusoids. The bile ducts were patent. Bile in the gall-bladder contained pigments and granules. No spleniculi were found. The right femur contained red bone marrow in the proximal half, but the distal half was spindle-shaped, containing gelatinous pale marrow, and there was subperiosteal new bone formation. The bone marrow was hypocellular, showing a considerable preponderance of normoblastic cells. Other viscera gave no apposite information. Our conclusion was haemolytic anaemia of unknown aetiology.'

Case 5. Paul B., aged 3 years 6 months, was admitted to the Watford and District Peace Memorial Hospital on June 11, 1947, under the care of Dr. A. White Franklin.

The patient was well until 10 days before admission, when he developed a sore throat and loss of appetite. Two days before admission he was jaundiced, and he vomited frequently. One day later his urine was noticed to be dark red. His past health and family history revealed nothing relevant.

On examination he was an apathetic, pale and jaundiced child. No abnormality was detected in the heart and lungs. The liver was just palpable; there was no enlargement of the spleen.

A blood count showed: Hb. 48%; red cells, 3,240,000; reticulocytes, 2%; leucocytes, 12,000 (neutrophils 64%, lymphocytes 26%).

In the red cell fragility test haemolysis began at 0·4% saline concentration and was complete at 0·28%. The blood urea was 53 mg.%. Urine contained 4 g.% albumin; the deposit showed occasional pus cells, epithelial cells, epithelial and granular casts; strong bands of methaemoglobin were seen on spectroscopic examination.

No growth of streptococci or diphtheroids was obtained from a throat swab.

On radiographic examination the long bones appeared normal.

In two days the haemoglobin value fell to 26%. The reticulocytes were then 4%, the platelets 500,000, leucocytes 39,500, and a blood smear showed anisocytosis, poikilocytosis and polychromasia. The Coombs test was negative.

In spite of daily blood transfusions haemolysis continued. The haemoglobin value remained low until the fifth day when it rose to 56%, when the reticulocytes were 45%. Thereafter, the urine was free from haemoglobin, and no further transfusion was required.

The serum Wassermann reaction and Kahn test performed on June 18 were positive. The tests were repeated one week later and were then negative. The sera of the parents gave negative results.

A pyrexia of 100 to 101° F. resolved after two weeks. The patient was discharged on July 1 when the haemoglobin had risen to 88%. He was well, and there had been no recurrence of the illness when seen two months later and again in May, 1951.

Review of the Literature and Discussion

In a comprehensive article on acute acquired haemolytic anaemia Dameshek and Schwartz (1940) referred to 100 cases of the idiopathic type reported by 80 different observers from 1907 to 1940.

Atkinson (1940) reviewed the literature up to 1938 and discovered 59 cases of 'Lederer's anaemia', 30 of which occurred in children.

Since 1940, 107 cases have been published, 68 of the patients being adults, and 32 children, 14 below the age of 1 year. In seven, the age was not given. The youngest patient affected was 6 weeks of age (Schoo, 1944); the oldest was a man of 77 years (Altschule and Gilligan, 1941).

It is evident that the disease may be met with at any age, but that the maximum incidence is during the first decade. Fifty per cent. of the adult cases recorded in the literature occurred in the third and fifth decades.

Sex Incidence. There was a slight preponderance of males in the proportion of 56 to 42. In nine the sex was not stated. Of the 32 children, however, 23 were males and nine females; a similar preponderance of the male sex in this age group was also noted by Atkinson (1940).

Seasonal Incidence. A possible allergic aetiology has been cited by some observers, one of whom (Battistoni, 1946) employed intradermal peptone injections in the treatment of a case. Hay fever as a concomitant symptom was reported by Mason (1942) in a girl of 15 years. In a review of 60 cases in which the date of onset of the disease was published, there was no significant variation in incidence during any season of the year.

Haemoglobinuria. Of 101 cases in which urine examination was mentioned, haemoglobinuria was present in 25, and 12 of these were children. One report (Stats, 1943) drew attention to the favourable prognosis in cases exhibiting haemoglobinuria Indeed, 22 of the above 25 cases recovered, and seven of these made a spontaneous recovery without intravenous blood transfusion or splenectomy.

The common occurrence of the symptom in children was alluded to by Atkinson (1940) and by Dameshek and Schwartz (1940). It was present in three of the cases reported here, all of which recovered.

Hepatosplenomegaly. Splenic enlargement is by no means a constant feature of the disease. It was absent in Cases 2, 3 and 5, slight in Case 4, and only temporarily present following a transfusion in Case 1. Of 81 cases in the literature in which the condition of the spleen was described, enlargement was present in 52. In 30 cases there was enlargement of the liver.

Auto-agglutination. This has been defined as the agglutination of a patient's red cells by his own serum, due to the presence of an agglutinin in the serum and a corresponding agglutinogen in the cells.

Despite the fact that Widal (1907) claimed this phenomenon to be constant and of diagnostic value in 'acquired haemolytic icterus', it escaped notice in the literature from 1914 until Davidson's paper in 1932. In 1936 Paterson and Smith published a case in which auto-agglutination occurred; it was also mentioned in the child described by Giordano and Blum (1937), and in one of the cases published by Greenwald (1938).

Renner (1947) found 115 cases of acute haemolytic anaemia of unknown aetiology on record in the literature, and the presence of auto-agglutinins was reported in 18, or 16%. He also listed 10 cases of acquired haemolytic anaemia associated with auto-agglutinins active at body temperature. The occurrence of the phenomenon at this temperature must be regarded as pathological. As Renner remarked, it was difficult to escape the conclusion that the agglutinins were responsible for red cell destruction *in vivo*, particularly as auto-agglutination had been found hitherto in connexion with haemolytic anaemias only (Lubinski, 1946). Kuhns and Wagley (1949) supported this hypothesis, and suggested that the auto-agglutination in their case contributed to intravascular thrombosis, and that both factors may have produced erythrostasis and further increase in blood destruction.

The association of auto-agglutination at 37° C, haemolytic anaemia, and multiple thromboses in

superficial leg veins and splenic vessels was noted by Young and Lawrence (1946) and by Renner (1947).

Of the five cases reported here, auto-agglutination at 37° C was present in Cases 1 and 2, it was absent in Cases 3 and 4, and was not tested for in Case 5. In Case 1 it was associated with a phenomenon suggestive of intravascular agglutination.

During the past ten years tests have been performed for auto-agglutinins in 38 recorded cases of acute haemolytic anaemia of idiopathic type. These were positive in 28, and in 10 the agglutinins were active at body temperature (Wiener, Reisner and Kalkstein, 1942; Evans, 1943; Lubinski, 1946; Renner and McShane, 1947; Ellis, Wollenman and Stetson, 1948; Tischendorf, Frank and Punin, 1948; Dacie, 1949; Kuhns and Wagley, 1949; Carter, Armstrong and Sydenstricker, 1949).

The significance of auto-agglutination as a primary aetiological factor in haemolytic anaemia has been disputed by Wiener (1942), who stated that it was a symptom and a result of the disease rather than the cause. A similar view was also held by Lubinski (1946), who considered that it was a test-tube reaction only, that it might be compared with the Weil-Felix reaction and the Paul-Bunnell test, and that its main importance lay in the fact that it was a source of error in blood grouping.

Haemolysins. These were first described by Chauffard and Troisier in 1908 and their occurrence in cases published in the literature was reviewed by Dameshek and Schwartz in 1940. The isohaemolysins found in the sera of two of their own cases were thought to bear some aetiological relationship to the haemolytic state; tests for autohaemolysins were not performed.

As the result of studies in the differentiation of acquired and congenital haemolytic anaemia, Neber and Dameshek (1947) affirmed that the acquired type was due to the action of a circulating autohaemolysin on the patient's red cells. It was present in the cases described by Currie (1944), Ellis *et al.* (1948), Dacie (1949) and possibly also by Reisner and Kalkstein (1942). In four of these auto-agglutinins were also found.

Since 1940, of 26 cases tested, isohaemolysins were detected in only two (Haydon, 1941; Dacie, 1949).

The Coombs, Mourant and Race Test. It was first observed by Boorman, Dodd and Loutit (1946) that the red cells of patients with acquired haemolytic anaemia give a positive direct Coombs test, and that this test could be used to differentiate the acquired from the congenital type of haemolytic anaemia. They described five cases in which the test was positive: (1) a Marchiafava-Micheli syndrome, (2) and (3) refractory anaemia with signs indicative of complicating haemolysis, (4) haemolytic anaemia secondary to malignant haemangiomata of liver and spleen and (5) chronic acquired haemolytic anaemia. This finding has since been confirmed by Evans and Duane (1949), who described a positive test in nine cases of acquired haemolytic anaemia, by Neber and Dameshek (1947) in one case, and by Kidd (1949) in six cases. There are in the literature an additional 14 references to cases of the acute idiopathic type of acquired haemolytic anaemia in which the Coombs test was positive (Denys and Van den Broucke, 1947, one case; Dacie, 1949, one case; Singer and Motulsky, 1949, seven cases; Selwyn and Hackett, 1949, two cases; Herweg, 1949, 2 cases; Piney, 1950, one case). The test was performed on the five cases reported here. In three it was positive (Nos. 1, 2 and 4) and a positive result persisted after resolution of the haemolytic process up to six weeks in Case 1 and seven weeks in Case 2, at which time the test had become negative. In Cases 3 and 5, however, a negative result was obtained. Such a finding must therefore not be taken to discountenance a diagnosis of acquired haemolytic anaemia. The latter view is corroborated by the work of Wright, Dodd, Bouroncle, Doan and Zollinger (1951). These authors reported that in 10 out of 58 cases of acquired haemolytic anaemia the Coombs test was negative, and a positive result was obtained in eight out of 25 cases of the congenital type. Singer *et al.* (1949) made a similar observation and stated that the value of the test in the differentiation of acquired and congenital haemolytic anaemia was thus diminished.

Wassermann Reaction. A positive Wassermann reaction in association with auto-agglutination in acute acquired haemolytic anaemia has been reported by various authors, one of whom, Lubinski (1946), suggested that there might be a common antigen for both these phenomena. The antigen for the Wassermann reaction consisted of lipid and protein, and, the author stated, that for the auto-agglutinins might be composed of a substance derived from protozoa, virus or toxic agents, and of some part of the red cells, one delivering the lipid and the other the protein. Both Wassermann reaction and Kahn tests were temporarily positive in Case 5 reported here.

Prognosis and Treatment. The treatment and outcome of cases culled from the literature since 1940 are illustrated in Table 1, and compared with the findings of other authors.

TABLE 1
COMPARISON OF RECOVERY RATE WITH METHOD OF TREATMENT

	All Cases		Group 1*		Group 2†		Group 3‡	
	Cases	Recovered	Cases	Recovered	Cases	Recovered	Cases	Recovered
Cases published (1940-1950)	94 total	72 (77%)	13	12 (92%)	41	32 (78%)	40	28 (70%)
	32 children	29 (91%)	7	7	21	18 (85%)	4	4
	62 adults	43 (69%)	6	5	20	14 (70%)	36	24 (67%)
Dameshek and Schwartz (1907-1940)	106	83 (78%)	24	13 (54%)	49	45 (92%)	33	25 (76%)
Carter *et al.* (1949)	67	53 (79%)	3	2	24	24 (100%)	40	27 (68%)

* Group 1. No treatment, or one or more of the following: subcutaneous, intramuscular, or intraperitoneal blood, liver extract, iron, vegetarian diet.
† Group 2. Blood transfusion only.
‡ Group 3. Blood transfusion and splenectomy.

Of a total of 94 cases of all ages, 77% recovered. Only three fatal cases were recorded in children, indicating a 91% recovery rate. Atkinson, in 1940, quoted a similar figure. A less favourable prognosis, however, must be tendered in adults, in whom the recovery rate was 69%. Dameshek and Schwartz (1940), in reviewing the literature up to 1940, found 106 cases and of these, 78% recovered. Approximately the same percentage was derived from a review of 67 cases collected by Carter *et al.* (1949).

In discussing treatment of the disease, the cases have been divided into three groups:

GROUP 1. Spontaneous recovery occurred in some (Roelsen and Ohlsen, 1945; Molinari Tosatti, 1945), and in others, recovery followed treatment with a vegetarian diet (Malten, 1940), liver extract (Hanssen, 1943; Canali, 1942), iron and liver extract (Smeenk, 1940), penicillin injections (Stefanutti, 1947), subcutaneous injections of blood (Schoo, 1944, two cases), intramuscular blood (Meier, 1943, two cases), intramuscular, intraperitoneal heparinized blood and vitamin K (Sterner, 1941). In all these 12 cases neither intravenous transfusion nor splenectomy was performed.

GROUP 2. The greater proportion of cases however required either one or more transfusions. Whole blood was usually employed, but Beard (1944) emphasized the value of plasma. An anti-haemolytic factor in normal human plasma was demonstrated by Josephs (1938), and two recoveries were reported by Gasser (1945) after plasma transfusions.

It was considered by most authors, however, that the disease was self-limiting, and that haemolysis was not directly influenced by blood transfusion. Many spontaneous cures were recorded (Currie, 1944; Parsons and Hawksley, 1933), and these probably coincided with the resolution of a primary unidentified lesion or metabolic disturbance (Loutit and Mollison, 1946).

Transfusion merely maintains a safe haemoglobin level while haemolysis continues. The duration of haemolysis varied from approximately four days in Cases 1, 2 and 3, to nine days in Case 5, and the number of transfusions necessary to correct the anaemia varied accordingly. Replacement transfusion employing 30 pints of blood was used in one case (Piney, 1950) with temporary good effect.

GROUP 3. With continuing haemolysis, splenectomy may cause a remission in some cases. Dameshek and Schwartz (1940) believe that the operation should be performed if three, or at most four, transfusions have not proved effective in controlling the disease. They stated that 100% mortality resulted from so-called expectant treatment. Dacie (1948) and Evans and Duane (1949), also advocated splenectomy, affirming that it offered the only hope of a real remission in the majority of patients.

The efficacy of this line of therapy was variable, and a group of cases occurred in which neither transfusion nor splenectomy was of any value in terminating haemolysis. Of 40 cases in which splenectomy was performed, 12 died. A similar mortality rate was reported by Carter *et al.* (1949), 50% of the deaths resulting from post-operative complications. In the cases recorded by Dameshek (1943), 50% of the fatalities were due to continuing haemolysis, and this was also responsible in Case 4 reported here, the patient dying one month following splenectomy despite repeated transfusions. Discouraging results have been reported by Thompson (1936), Dyke and Young (1938) and Haydon (1941).

From Table 1 it is evident that in 90 patients

receiving intravenous transfusion alone the survival rate was 86%; while of 73 who underwent splenectomy 72% recovered. It may be concluded that operative treatment is of value for those patients in whom continued transfusion is no longer practicable.

Many cases have been published in which recovery followed repeated transfusions and in which splenectomy was not performed (Kettner, 1947; Ellis *et al.*, 1948; Buch, 1948; Selwyn and Hackett, 1949; Herweg, 1949). In one (Loutit and Mollison, 1946) the patient declined operation and subsequently recovered.

Encouraging reports have recently appeared regarding the use of A.C.T.H. in the treatment of acquired haemolytic anaemia. Improvement followed in five cases (Gardner, 1950; Dameshek, 1950), and recovery in one case (Davidson, Duthie, Girdwood and Sinclair, 1951), a dose of 100 mg. daily for 10 days being employed in the latter. Little or no response resulted from this therapy in two cases of congenital haemolytic anaemia.

Aetiology. Although auto-agglutinins or auto-haemolysins may explain the mechanism of the anaemia in some cases, the primary cause or stimulus to the production of these antibodies remains an enigma. One theory advanced by Lubinski (1946) was that the antigen for auto-agglutinins might be composed of a substance derived from protozoa, toxic agents or viruses, and of some part of the red cells. Another (Mendell, Meranze and Meranze, 1936) proposed that a circulating toxin was perhaps the aetiological factor suggested by the presence of degenerative granules within a large number of the granulocytes.

Erythrophagocytosis by monocytes in the peripheral blood was reported by Landolt (1946) and by Hargraves, Herrell and Pearman (1941).

In Cases 1 and 2 the patients had been in contact with respiratory infections of probable virus origin, and both had symptoms of upper respiratory tract infection. Chest radiographs revealed no abnormality, but virus infection was a possible aetiological factor in these two instances.

Summary

The diagnostic criteria of acute idiopathic haemolytic anaemia are defined.

Five cases of the disease occurring in children are reported, two of which showed auto-agglutination at body temperature.

One hundred and seven case reports published since 1940 are analysed, and the literature reviewed, with particular reference to cases in children.

The significance of auto-agglutination at 37° C is discussed, and references to 10 cases of this disease showing the phenomenon are given.

A negative Coombs test in two cases is reported, and the value of the test in differentiating the congenital and acquired types of haemolytic anaemia is discussed.

A recovery rate of 90% is to be expected in children, and 70% in adults.

Spontaneous recovery may occur but most patients require transfusion. A proportion of those exhibiting continuing haemolysis in whom transfusion is no longer practicable may show a remission following splenectomy.

The aetiology of the disease is briefly discussed.

I wish to thank Dr. W. G. Wyllie for his encouragement, advice and permission to publish Cases 1, 2 and 3. My thanks are also due to Dr. I. A. B. Cathie for his helpful criticism, and to Dr. Donald Paterson and Dr. A. White Franklin for allowing me to publish Cases 4 and 5 respectively.

References

Altschule, M. D. and Gilligan, D. R. (1941). *Arch. intern. Med.*, **68,** 957.
Atkinson, F. R. B. (1940). *Brit. J. Child. Dis.*, **37,** 35.
Battistoni, L. (1946). *Clin. nuova*, **2,** 176.
Beard, M. F. (1944). *Sth. med. J.* (*Bgham., Ala.*), **37,** 448.
Boorman, K. E., Dodd, B. E. and Loutit, J. F. (1946). *Lancet*, **1,** 812.
Buch, H. (1948). *Acta. med. scand.* (supp. 213), 99.
Canali, G. (1942). *Haematologica*, **24,** 469.
Carter, C. H., Armstrong, E. S. and Sydenstricker, V. P. (1949). *J. med. Ass. Ga.*, **38,** 52.
Chauffard, M. A., Troisier, J. and Vincent, C. (1908). *Sem. méd., B. Aires*, **28,** 345.
Currie, J. P. (1944). *Brit. med. J.*, **2,** 8.
Dacie, J. V. (1949). *Blood*, **4,** 928.
Dameshek, W. (1950). *Blood*, **5,** 791.
—— (1943). *Clinics*, **2,** 118.
—— and Schwartz, S. O. (1940). *Medicine*, **19,** 231.
Davidson, L. S. P. (1932). *Quart. J. Med.*, **25,** (n.s. 1), 543.
——, Duthie, J. J. R., Girdwood, R. H. and Sinclair, R. J. G. (1951). *Brit. med. J.*, **1,** 657.
Denys, P. and Van den Broucke, J. (1947). *Arch. franç. Pédiat.*, **4,** 205.
Dyke, S. C. and Young, F. (1938). *Lancet*, **2,** 817.
Ellis, L. B., Wollenman, O. J. and Stetson, R. P. (1948). *Blood*, **3,** 419.
Evans, R. S. (1943). *Stanford med. Bull.*, **1,** 178.
—— and Duane, R. (1949). *Calif. Med.*, **70,** 244.
Gardner, F. (1950). *Blood*, **5,** 791.
Gasser, C. (1945). *Helv. paediat. Acta.*, **1,** 38.
Giordano, A. S. and Blum, L. L. (1937). *Amer. med. Sci.*, **194,** 311.
Greenwald, H. M. (1938). *Ibid.*, **196,** 179.
Haydon, R. L. (1941). *Surg. Clin. N. Amer.*, **21,** 1453.
Hanssen, P. (1943). *Acta. med. scand.*, **113,** 251.
Hargraves, M. M., Herrell, W. E. and Pearman, R. O. (1941). *Proc. Mayo Clin.*, **16,** 107.
Herweg, J. (1949). *J. Pediat.*, **35,** 637.
Josephs, H. W. (1938). *Bull. Johns Hopk. Hosp.*, **62,** 53.

Kettner, M. (1947). *Z. Kinderheilk.*, **65,** 1.
Kidd, P. (1949). *J. clin. Path.*, **2,** 103.
Kuhns, W. J. and Wagley, P. F. (1949). *Ann. intern. Med.*, **30,** 408.
Landolt, R. F. (1946). *Helv. paediat. Acta.*, **1,** 335.
Lederer, M. (1925). *Amer. J. med. Sci.*, **170,** 500.
—— (1930). *Ibid.*, **179,** 228.
Loutit, J. F. and Mollison, P. L. (1946). *J. Path. Bact.*, **58,** 711.
Lubinski, H. and Goldbloom, A. (1946). *Amer. J. Dis. Child.*, **72,** 325.
Malten, H. (1940). *Münch. med. Wschr.*, **87,** 1207.
Mason, V. R. (1942). *Trans. Ass. Amer. Phys.*, **57,** 234.
Meier, K. (1943). *Ann. paediat.* (*Basel*), **161,** 244.
Mendell, T. H., Meranze, D. R. and Meranze, T. (1936). *Amer. J. med. Sci.*, **192,** 316.
Molinari, P. Tosatti (1945). *Haematologica*, **27,** 337.
Neber, J. and Dameshek, W. (1947). *Bull. New Engl. med. Cent.*, **9,** 166.
Parsons, L. G. and Hawksley, J. C. (1933). *Archives of Disease in Childhood*, **8,** 184.
Patterson, W. H. and Smith, G. S. (1936). *Lancet*, **2,** 1096.
Piney, A. (1950). *Sang.*, **21,** 229.
Reisner, E. H. and Kalkstein, M. (1942). *Amer. J. med. Sci.*, **203,** 313.
Renner, W. F. and McShane, J. R. (1947). *Sth. med. J.* (*Bgham. Ala.*), **40,** 973.
Roelsen, E. and Ohlsen, A. Soeborg (1945). *Acta med. scand.*, **122,** 60.
Schoo, A. (1944). *Ann. paediat.* (*Basel*), **163,** 51.
Selwyn, J. G. and Hackett, W. E. R. (1949). *J. clin. Path.*, **2,** 114.
Singer, K. and Motulsky, A. G. (1949). *J. Lab. clin. Med.*, **34,** 768.
Smeenk, C. (1940). *Ned. Tijdschr. Geneesk.*, **84,** 1822.
Stats (1949). *J. Pediat.*, **34,** 105.
Stefanutti, P. (1947). *Policlinico* (*prat.*), **54,** 1157.
Sterner, L. G. (1940). *Acta. paediat.*, **28,** 196.
Thompson, W. P. (1936). *J. Amer. med. Ass.*, **107,** 1776.
Tischendorf, W., Frank, A. and Punin, W. (1948). *Klin. Wschr.*, **26,** 262.
Widal, F., Abrami, P. and Brulé, M. (1907). *Pr. méd.*, **15,** 641.
Wiener, A. S. (1942). *Amer. J. clin. Path.*, **12,** 189.
Wright, C. S., Dodd, M. C., Bouroncle, B. E., Doan, C. A. and Zollinger, R. M. (1951). *J. Lab. clin. Med.*, **37,** 165.
Young, L. E. and Lawrence, J. S. (1946). *Arch. intern. Med.*, **77,** 151.

Bibliography

Acuna, M. and Gambirassi, A. C. (1942). *Arch. argent. Pediat.*, **17,** 421.
Amado, P. (1948). *Gaz. méd. portug.*, **1,** 5.
Arcuri, F. and Chiti, E. (1948). *Arch. "Maragliano" Patol. Clin.*, **3,** 433.
Bindschedler, Apffel and Adrian (1946). *Arch. franç. Pédiat.*, **3,** 89.
Castellanos, A. and Montero, R. (1940). *Arch. Soc. Estud. clin. Habana*, **34,** 387.
—— —— (1940). *Arch. Med. interna.*, **6,** 232.
Cheney, G. and Denenholz, E. J. (1945). *Med. Clin. N. Amer.*, **29,** 695.
D'Alessandro, G. (1940). *Policlinico* (*prat.*), **47,** 1035.
David, J. K. and Minot, A. S. (1944). *Amer. J. Dis. Child.*, **68,** 327.
Fisher, J. A. (1947). *Quart. J. Med.*, **16,** 245.
Fontan, Verger, P. and Féraut (1947). *Arch. franç. Pédiat.*, **4,** 33.
Germini, P. (1946). *Policlinico* (*prat.*), **53,** 527.
Hoyer, K. (1941). *Nord. Med.* (*Hospitalstid*), **1,** 3387.
Jones, C. S. (1945). *S. Afr. med. J.*, **19,** 470.
Kjellberg, K. (1941). *Kinderärztl. Praxis.*, **12,** 296.
—— (1942). *Nord. Med.*, **14,** 1692 (abstr. of above).
Meier, K. (1944). *Ann. paediat.* (*Basel*), **162,** 140.
Metzger, H. and Lévy, J. G. (1948). *Paris méd.*, **38,** 337.
Mollison, P. L. (1947). *Clin. Sci.*, **6,** 137.
Moser, P. and Spielmann, W. (1950). *Z. ges. inn. Med.*, **5,** 417.
Novelli, E. (1947). *Arch. "Maragliano" Patol. Clin.*, **2,** 525.
Papayannopoulos, G. (1947). *Brit. med. J.*, **2,** 371.
Pavlovsky, A. and Quirno, N. (1943). *Dia. med.*, **15,** 190.
Rao, S. V. and Rao, A. S. (1940). *Antiseptic*, **37,** 1087.
Sabta, G. (1946). *Haematologica*, **29,** 399.
Schrifrin, N. (1949). *J. Pediat.*, **34,** 103.
Spira, M. (1943). *Z. Kinderheilk.*, **64,** 187.
Ytrehus, O. (1947). *Nord. Med.*, **34,** 1113.

THE PATHOLOGY AND BIOCHEMISTRY OF GARGOYLISM

A REPORT OF THREE CASES WITH A REVIEW OF THE LITERATURE

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The detailed study by Lindsay, Reilly, Gotham and Skahen (1948) of the pathology in 12 cases of gargoylism was a welcome addition to the literature on the pathology of this curious disease. The study of the pathological features in such a relatively large series of cases enabled these workers greatly to amplify the pathological picture, which had previously been based on a small number of isolated reports. A few additional pathological reports have recently been published making a total of 12 detailed and 10 incomplete reports, with, in addition, several biopsy reports.

Lindsay and his colleagues gave a detailed description of the pathology in seven of their cases, incomplete data from another fatal case, and biopsy studies from four cases; the first of the seven detailed reports had been published by Reilly (1935), but some of the histological features now known to be characteristic were not recognized at that time. The antecedent literature contains 12 earlier post-mortem reports, only six of which are reasonably complete; also several biopsy studies. The six reasonably comprehensive reports published before the appearance of the notable contribution by Lindsay and his colleagues were written by Reilly (1935), Kressler and Aegerter (1938), who published the first detailed account of the pathology in a typical case of the disease, De Lange (1942), Kny (1942), De Lange, Gerlings, De Kleyn and Lettinga (1944) and Strauss (1948). A detailed report on the brain of the last of these cases was reported by Green (1948). The incomplete reports by Tuthill (1934) on one of Hurler's cases, and Ashby, Stewart and Watkin (1937) on two cases, were chiefly concerned with the nervous system. The other incomplete pathological reports were by Stoeckel (1941), Wolff (1942) and Njå (1945). Recently, reports on four more cases have been published: Lindsay (1950) gave a detailed account of the features in an infant aged 4½ months, Magee (1950) an incomplete report on one case and Jervis (1950) incomplete reports on two cases. Reports on the pathology of the cornea were contributed by Berliner (1939), Rochat (1942) and Zeeman (1942), each one case, and by Cordes and Hogan (1942), three cases. The full pathological reports of two of these cases were included in the series of Lindsay *et al.* (1948). Biopsy examinations were reported by Ellis (1937) on the liver and spleen; by Reilly (1935) and Debré, Marie and Thieffry (1946) on the liver; and by Höra (1939), and Schmidt (1942) on bone. A few other pathological reports may have been overlooked.

Strauss, Merliss and Reiser (1947) in a paper on gargoylism recorded a detailed pathological and biochemical examination in a man aged 29 years who was regarded by the authors as a case of this disease. There were so many atypical clinical and pathological features that the case cannot be accepted with certainty as one of gargoylism, though it may well have been a *forme fruste*. The patient appeared normal until after the age of 9 years, a most exceptional circumstance; he then developed progressive coarsening of the features, limitation of movement of the joints, deformity of the limbs and stunting. This case has been excluded from the following review of the pathology of gargoylism because of its doubtful classification.

We have had the opportunity of studying the pathological features of gargoylism in three young children who were observed at the Royal Hospital for Sick Children, Edinburgh, during recent years. One died in the hospital and complete post-mortem and histological examinations were made (A.R.M.); also a differential lipoid analysis of the liver and spleen (S.J.T. and R.H.). The other two children had a biopsy examination made of certain organs. Some of the pathological features in the first of these three cases, notably the vascular infiltration and the heavy meningeal deposit, were of particular interest to us when we observed them in 1944, as neither had been described in the literature at that time.

CASE RECORDS

Case 1. A.McA., a boy, died on April 28, 1944, aged 6 years.

The father, aged 41 years, and the mother, aged 30 years, appeared healthy, also an elder brother aged 12 years and a younger brother aged 4 years. There had been no miscarriages. There was no history of physical or mental peculiarities on either side of the family, or of consanguinity.

Antenatal development was apparently normal. Delivery was by breech and the infant's condition was apparently satisfactory at birth. The mother thought that development was normal until the age of 9 months, when she noticed numerous abnormalities. 'His head seemed big in comparison with his body, and his body in comparison with his legs. His legs were thin. His tongue protruded.' An umbilical hernia was becoming perceptible at that time and a left inguinal hernia, present since birth, had become much larger. At 15 months he was admitted to the Royal Hospital for Sick Children, Glasgow, for operative treatment of the left inguinal hernia. The mother was told that he was mentally backward. He began to feed himself at 1½ years and to walk with assistance at 2 years.

At 3 years and 4 months he was recommended to the Ear, Nose and Throat Department, Royal Hospital for Sick Children, Edinburgh, for removal of his adenoids but was transferred to a medical ward for investigation of his general condition. At that time he was 34¼ in. in height and 32 lb. in weight; dentition was still incomplete and he could walk alone, though very unsteadily. The umbilical hernia had become larger. A diagnosis of gargoylism was made. At 6 years he was again admitted to the Royal Hospital for Sick Children, Edinburgh. He was still doubly incontinent; he had not begun to talk nor did he appear to understand speech. He could make himself understood by his mother and seemed to understand the significance of preparations such as for a meal or for going out. He was said to be happy and contented, not destructive, to look at books and to play with toys.

FIG. 1. FIG. 2.

FIG. 1.—A. McA., aged 3½ years. A typical example of gargoylism.
FIG. 2.—A. McA., aged 6 years. This picture taken five weeks before death shows increased malformation of the chest and greater flexion deformity of the elbows, also a severe degree of emaciation.

A dwarfed boy (Figs. 1 and 2), he was now 37½ in. in height, with a big head, an ugly face, a short neck, a deformed thorax, a protuberant abdomen with a large umbilical hernia, a lumbo-dorsal kyphosis, limbs incapable of complete extension and genu valgum.

The head was large (occipito-frontal circumference 23 in., anterior fontanelle closed). The frontal region was broad and prominent and there was slight bulging of the temporal bones above the ears. Fairly deep vascular channels could be felt, especially in the fronto-parietal regions and in the vicinity of the occipital protuberance. A large varicose vein extended from the latter situation to the right ear. The ears were large, as big as an adult's. The ugly face showed rather shallow orbits with a very flat nose bridge and a button-like nose, with broad alae nasi and round nostrils constantly discharging mucopus. A red polyp the size of a pea projected slightly from and occluded the right nostril. The mouth looked a little large and the tongue was usually protruding. The lips were not unduly thick. The mandible looked broad and heavy for a boy of his age. The teeth were widely spaced in both mandible and maxilla and most of them were poorly calcified. The tongue was enlarged, usually protruded, and showed abnormal dorsal fissuring; it was not sucked.

The neck was very short so that the head appeared to be planted on the shoulders.

The trunk also showed numerous abnormalities. The antero-posterior diameter of the thorax was greatly increased and equal to the lateral diameter. The upper part of the sternal body was unduly prominent and the lower part was turned backwards. There were Harrison's sulci. The visible ribs looked broad. The abdomen was protuberant and rounded and rested on his thighs as the child sat in bed. There was a large umbilical hernia about 2½ in. in diameter. The hernial ring admitted two fingers. The penis and testes appeared normal but a varicocoele was observed on the right side. There was a pronounced angular kyphosis in the dorso-lumbar spine. The scapulae were small and unusually highly and laterally placed; the inferior angle reached the sixth rib. The arms were abnormally short and the hands looked broad.

The limbs could not be fully extended. Abduction of the shoulders caused rotation of the scapulae towards the axillae; an angle exceeding 90° between humeri and scapulae could not be attained. Elbow extension was reduced by about 30° and supination of the forearm was moderately limited, also dorsiflexion of the wrists. Complete extension of the fingers was impossible and all were radially deviated and rotated a little towards the thumb; there was slight claw-hand. The hands

looked wide because of the short fingers. The finger nails also were short and wide looking. The legs showed a slight degree of limitation of extension at the knees and hips but other movements at the hips did not show any appreciable restriction. There was genu valgum, pronounced on the left and slight on the right. The toes were broad and rather stumpy like the fingers. On standing, the knees touched and were slightly flexed.

The skin was rather dry and its elasticity rather poor. The cheeks were ruddy. The dark brown hair was unusually coarse, also the eyebrows, the hairs of which projected unduly. The eyebrows met in the midline. The eye lashes were normal. The lips and conjunctivae had a normal colour. There was a purulent discharge from the left ear from which *Staph. aureus* and diphtheroids were obtained by film and culture; the left tympanic membrane was perforated. There was a bilateral diffuse corneal opacity which imparted a ground glass appearance to the eyes.

Nutrition was poor (weight, 38¾ lb.). There was a subnormal amount of subcutaneous fat. The limbs were all thin, especially the legs. The calves were very thin.

MUSCULAR CONDITION. The general muscle volume was poor, particularly noticeable in the calves. The general tone was poor. He did not like to stand indefinitely and walked with difficulty when holding a finger. When he clapped his hands the movements were slow and clumsy.

MENTAL CONDITION. He was severely mentally defective. He shouted and periodically made loud noises which sometimes resembled singing. He attracted people's attention, for example to point out a light. He could drink from a cup and eat with his hands but could not feed himself with a spoon. He resented examination in a fairly normal manner and became annoyed when made to do certain things such as lying down. He laughed when tickled. He was doubly incontinent.

ALIMENTARY SYSTEM. The liver was considerably enlarged extending to four fingerbreadths below the costal margin in the mid-clavicular line. The spleen was slightly enlarged and could be palpated one fingerbreadth below the costal margin.

CARDIOVASCULAR SYSTEM. The heart was moderately enlarged. The apex beat was in the sixth intercostal space 1 in. lateral to the mid-clavicular line. There was a soft mitral systolic murmur and reduplication and accentuation of the pulmonary second sound. A radiograph of the heart showed considerable enlargement, particularly of the left ventricle.

RESPIRATORY SYSTEM. There was a considerable amount of thickish, muco-purulent discharge from both nostrils and a similar post-nasal discharge. The nasal polypus projecting from the right nostril has been noted. There was mouth breathing with snoring.

X-RAY EXAMINATION OF SKELETON. The skull bones were not thickened; the vascular channels were unduly prominent and the sella turcica was large. The ribs had narrow necks and wide bodies. The bodies of the last two thoracic and second lumbar vertebrae were dysplastic. The eleventh thoracic vertebra showed considerable hypoplasia of the body. The twelfth thoracic vertebra also showed a small body with an

FIG. 3.—Lateral radiograph of dorso-lumbar spine in Case 1, showing typical hook-like malformation of the body of the twelfth dorsal vertebra, also to a lesser degree of the bodies of the eleventh dorsal and second lumbar vertebrae. The broad ribs are also typical.

anterior defect in its upper half, showing in the lateral view. This imparted a hook-like appearance to the vertebral body. The second lumbar vertebra also showed a rather small body and a less pronounced but characteristic hook-like deformity (Fig. 3). This deformity occurs in one or more of the vertebrae from the eleventh thoracic to the second lumbar in a high proportion of cases of gargoylism and is a pathognomonic feature of the disease.

The limb bones were characteristically thickened and roughly formed. The humeral and femoral heads were somewhat flattened. The humeral necks were narrow and there was a medial bending of the shafts of the humeri at the neck. The irregular outline of the bases of the metacarpals and the claw-hand were clearly seen (Fig. 4). The normal number of carpal

FIG. 4.—Radiograph of forearm and hand of Case 1, showing typical thickening and irregularity of the long bones.

bones was present, but several of them were unusually small and were probably late in appearing.

Arrangements were made to repair the umbilical hernia by operation. On April 28, 1944, phenobarbitone, grains 2, and atropine sulphate, grains 1/100, were given before an attempt was made to induce anaesthesia with nitrous oxide and oxygen. After a small amount of anaesthetic had been administered he became very cyanosed and breathing ceased. Respiration began again with the aid of artificial respiration; no further anaesthetic was given, and the operation was abandoned. The cyanosis disappeared and on becoming conscious the child became restless and cried. After about two hours he suddenly collapsed and became pale, cyanosed and pulseless. Artificial respiration, adrenalin 5 m. and coramine 1 ml. intracardially, were of no avail and he soon died.

Post-mortem Report

The general appearance was as has already been described.

Head. The bones of the vault of the skull were of average thickness and density. The mandible was thick and heavy; thickening was especially noticeable at the symphysis menti, where the antero-posterior diameter of the bone was much increased. The increased thickness of the rami decreased the space between their inner surfaces, so that the size of the oral cavity was reduced.

Meninges. Adhesions were present between the dura mater and the pia-arachnoid over the vertex of the brain. Over this area there was a deposit of yellowish material, which adhered to the inner surface of the dura and to the arachnoid.

The leptomeninges showed a peculiar greyish opacity, which intensified to whiteness over the temporal poles. The subarachnoid space was slightly enlarged and contained a quantity of gelatinous material.

Brain. The brain was large (1,758 g.). Externally, there was no evidence of swelling or atrophy. The arteries at the base showed white flecks in their walls resembling atheromatous deposits.

On section, a moderate degree of atrophy of the white matter was found, with dilatation of the lateral and third ventricles. The perivascular spaces in the subcortical regions of the cerebral hemispheres were enlarged and contained gelatinous material similar to that in the subarachnoid space. This condition was most pronounced in the upper lateral occipital regions.

Serous Sacs. The pleural, pericardial and peritoneal sacs were healthy.

Respiratory System. No abnormality was found in the respiratory passages. The lungs were congested and slightly oedematous. No pneumonia was present.

Cardiovascular System. The heart was slightly enlarged, owing to hypertrophy of the left ventricle. None of the chambers was dilated. The colour and consistence of the myocardium were not abnormal. The coronary arteries were straight, prominent and hard. To the touch they felt like nodular cords, and they were studded with numerous small, pale yellow flecks. Not only the main branches, but even the smallest visible twigs on the surface of the heart were affected in this way.

Both cusps of the mitral valve were thick and opaque. At the points of attachment of the chordae tendineae there were prominent fibrous nodules. The cusps and the chordae were not contracted or distorted, and the orifice was not stenosed. The cusps of the aortic valve also were thick and opaque, but this change was less pronounced than in the mitral valve. The tricuspid and pulmonary valves were not affected.

Alimentary System. The tongue was very large, being of average adult size, heavily furred and fissured.

No abnormality was noted in the pharynx or oesophagus.

The umbilical hernia contained neither bowel nor omentum. The alimentary tract presented no abnormality. The liver was much enlarged (1,150 g.), uniformly pale brown, and fairly firm. The pancreas showed no abnormality.

The Spleen. The spleen was slightly enlarged (83 g.). Its consistence was not altered. The cut surface was greyish red. The Malpighian bodies were visible but small.

Urogenital System. The left kidney and ureter were normal. The right kidney was much enlarged (8 in. long; 723 g.). This was due to severe hydronephrosis. The immensely dilated pelvis contained clear fluid. The renal substance was atrophied so much that only a thin membrane remained. The right ureter was sharply kinked immediately below the pelvi-ureteric junction, where it described a hair-pin bend, the limbs of which were bound together by connective tissue. Below this kink the ureter was of normal calibre. The bladder was healthy.

Both testicles were in the scrotum and appeared healthy.

Endocrine Glands. The pituitary gland was enlarged (0·85 g.), and lay in a somewhat enlarged pituitary fossa.

The right suprarenal gland weighed 3 g. It had been compressed between the liver and the enlarged right kidney and was flattened. The left suprarenal gland weighed 3·52 g. and appeared healthy. The thyroid, parathyroid and thymus glands showed no obvious abnormality.

The Bones. Portions of the limb bones that were examined were not visibly abnormal and contained marrow of normal appearance. The ribs showed slight ' beading ' of the costochondral junctions on the inner aspect, and some a slight flat bulge extending about 1 cm. along the inner surface of the rib from the junction.

The bodies of the lower dorsal and upper lumbar vertebrae, at the site of the kyphosis, were reduced in size from above downward, but on section the bone did not appear to be abnormal.

Histological Report

Liver (Figs. 5 and 6). In paraffin sections all the parenchymal cells had a foamy appearance, owing to the presence of vacuoles in the cytoplasm, from which some material had been dissolved out in the process of preparation. The vacuoles varied in size, but were mostly small. They were less sharply defined than the vacuoles that are found in ordinary fatty degeneration. The nuclei had not been compressed and many retained their central position in the cells. The swelling of the liver cells had compressed the sinusoids, so that many had become almost indistinguishable. The Kupffer cells were inconspicuous, but some had foamy cytoplasm, as if they too contained the abnormal substance. The fibrous stroma and the blood vessels were normal.

Spleen. Endothelial (Fig. 7) cells attached to the walls of the sinusoids of the pulp were swollen and had vacuolated cytoplasm, so that the sinusoids appeared to be lined by a continuous layer of large, pale, foamy cells. A few similar cells lay free in the lumina of the sinusoids. The swelling of the littoral cells decreased the lumina, so that the pulp had a solid appearance. No foamy cells were seen between the sinusoids. In the Malpighian bodies, which were of average size, a few foamy cells were observed in the lymphoid reticulum. Some of the Malpighian arterioles showed hyaline degeneration of their walls.

Heart. In a few places small, round cells were found in the fibrous septa of the myocardium, which was otherwise unaltered. The pericardium was healthy. The mural endocardium was not altered. The anterior cusp of the mitral valve was increased in thickness throughout its length (Fig. 8). This was caused by a development of dense fibrous tissue, among which were swollen, vacuolated cells. The number of these foamy cells varied from place to place and was inversely proportional to the amount and density of the fibrous tissue. In the most fibrous parts they lay singly, separated by fibrous tissue, and many had a degenerated appearance; sometimes only remnants of dead cells were recognizable in spaces between the fibrous bundles. In one place at the base of a cusp, old hyaline fibrous tissue had been calcified.

Arteries. The coronary arteries on the surface of the heart showed striking changes (Figs. 9 and 10). The intima was immensely thickened in an almost uniform, concentric manner, so that the lumen was greatly reduced. The thickened intima was composed of fibrous tissue, in the interstices of which were numerous large foamy cells. The surface endothelium was intact. The internal elastic lamina could be traced round most of the circumference, but had suffered fragmentation at a few points. The media was stretched and thin and had been slightly invaded by foamy cells, especially in the inner part, immediately external to the elastic lamina, but here and there also in the outer part. The radial, brachial (Fig. 11) and anterior tibial arteries showed changes of the same nature as those in the coronary arteries, but differing in two respects: the intimal thickening was not concentric, but more on one side than the other, and the abnormal tissue that was responsible for it was more densely fibrous and contained fewer foamy cells.

The axillary artery showed no pathological changes.

Dura Mater. The deposit on the inner surface of the dura mater was composed of sheets of foamy cells, with a small amount of supporting fibrous tissue and blood vessels (Figs. 12 and 13).

Brain. Sections were taken from the frontal, central and occipital cortex, basal ganglia, cornu ammonis, midbrain, cerebellum, medulla, spinal cord, choroid plexus, basilar artery and peripheral nerve. The peripheral nerve, choroid plexus and basilar artery were healthy. All the other parts showed similar changes. In all the nerve cells, especially the larger ones, in the cortex, basal ganglia, brain stem, cerebellum and spinal cord, there were intracytoplasmic granules of a substance that was isotropic and did not stain with Scharlach red. In some cells the Nissl substance was evenly distributed amongst the granules; in others it lay peripherally in a concentric or eccentric manner. The nerve cell population was not affected, except in the substantia nigra, where one cell was found degenerating and undergoing phagocytosis. Histiocytes containing deposit were present in the perivascular spaces. In the cerebral white matter, especially, this was associated with a wide, net-like, concentric distension of the adventitia of the blood vessels, as if abnormal material were lying in an extracellular position. In the subarachnoid space there were moderately numerous histiocytes, and distension of the subarachnoid meshes by extracellular material was a striking feature.

Lymph Nodes. Nodes from various situations showed many foamy cells in the lumina, and attached to the walls, of the sinuses throughout the glands. Some of the sinuses were crowded with these cells (Fig. 14).

Thymus Gland. This showed foamy cells in considerable numbers in the medullary portions, especially in relation to blood vessels, but these were scanty in the cortical parts.

Intestine (Ileum). A few foamy cells were found in the lymphoid tissue of a Peyer's patch.

Testis. In the interstitial tissue were numerous foamy cells. Their presence caused the tubules to be more widely separated than usual.

Pituitary Gland. Most of the cells in the pars anterior had a foamy character (Fig. 15). Normal pituitary cells were scanty and mostly of oxyphil type. The pars posterior was not affected.

Eye. Small deposits of foamy cells were found in the cornea and in the sclera, especially near the corneo-scleral junction. No other abnormality was noted.

Lung. The lung was oedematous. In the alveoli were many histiocytes containing dust particles. No foamy cells were present.

Kidney. The kidney showed no specific changes. Fatty degeneration affected the cells of the loops of Henle.

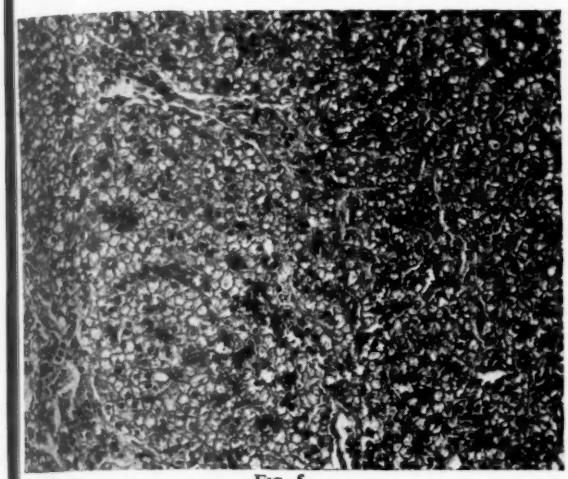

FIG. 5.

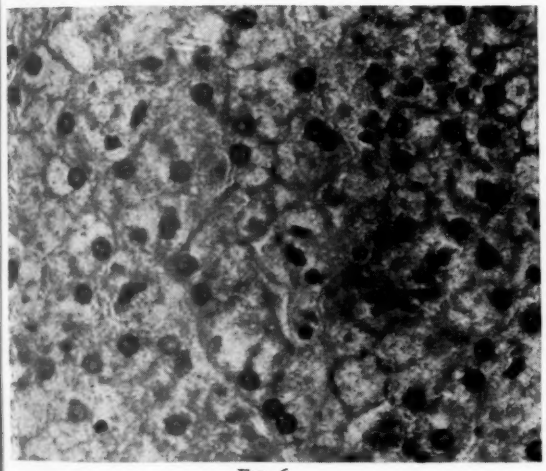

FIG. 6.

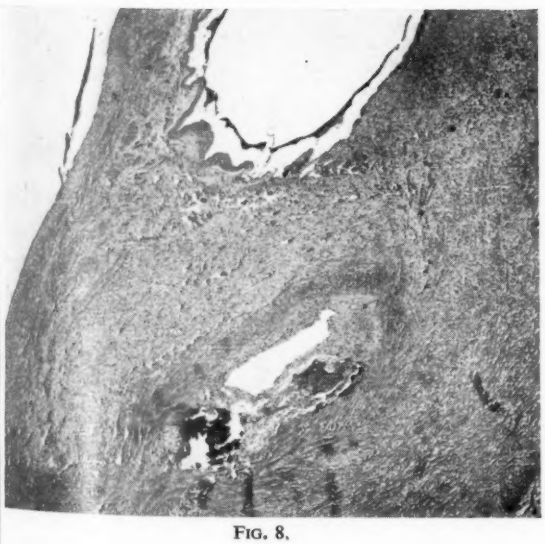

FIG. 8.

FIG. 5.—Liver section in Case 1. The epithelial cells are swollen and vacuolated and the sinusoids have been compressed and are inconspicuous. H. & E. × 100.

FIG. 6.—Liver in Case 1. H. & E. × 400.

FIG. 7.—Spleen in Case 1. The endothelial cells lining the sinusoids are swollen and vacuolated. Most of them remain attached to the walls. H. & E. × 400.

FIG. 8.—Mitral valve cusp in Case 1. The area shown is at the base of the anterior cusp. There is great thickening, with dense fibrous tissue containing foamy cells. Calcification has occurred in a small area. H. & E. × 13.

FIG. 9.—The coronary artery in Case 1. The intima is thickened all round the circumference with fibrous tissue containing many foamy cells. The lumen is greatly reduced. H. & E. × 45

FIG. 10.—The coronary artery in Case 1. Part of intima shown in Fig. 9 to show detail of abnormal tissue. H. & E. × 400.

FIG. 11.—Brachial artery in Case 1. The intima is greatly thickened on one side by fibrous tissue containing many foamy cells, and the lumen is much reduced. H. & E. × 13.

FIG. 12.—Dura mater in Case 1. The deposit on the inner surface is composed of sheets of vacuolated histiocytes. H. & E. × 100.

FIG. 13.—Dura mater in Case 1. High power view of part of field shown in Fig. 12 to show detail of the foamy cells. H. & E. × 400.

FIG. 14.—Mesenteric lymph node in Case 1. The sinus endothelium has proliferated and fills dilated sinuses. All these cells have a foamy character. H. & E. × 400.

FIG. 15.—Pituitary gland, pars anterior in Case 1. Most of the cells are distended and vacuolated. The few normal cells are mostly of eosinophil type. H. & E. × 400.

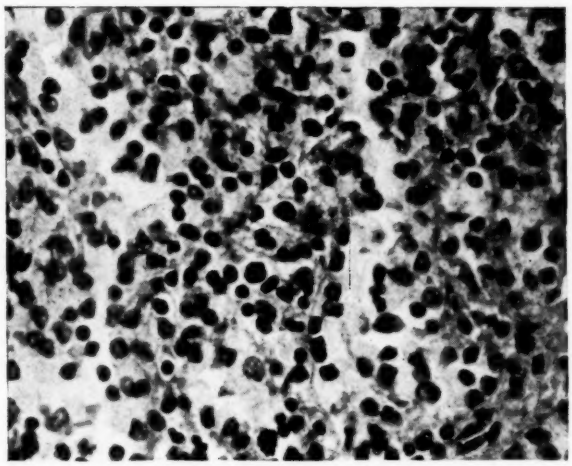

FIG. 7.

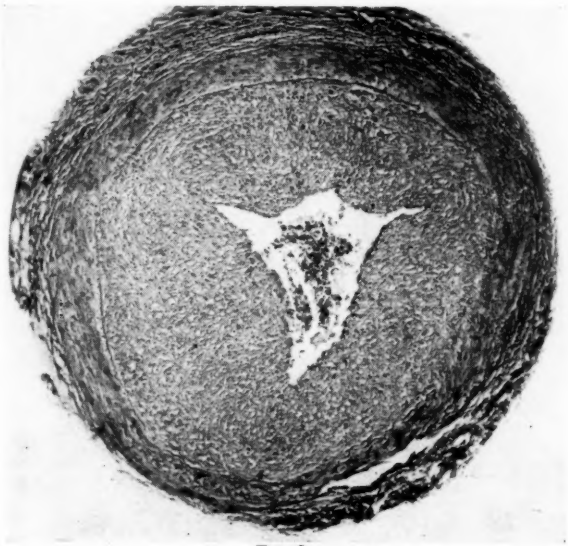

FIG. 9.

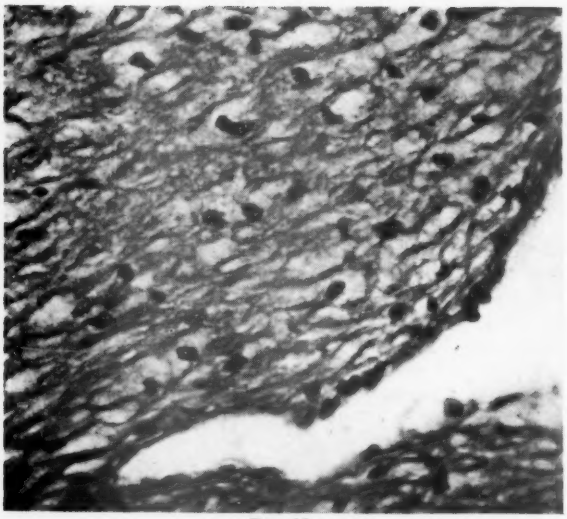

FIG. 10.

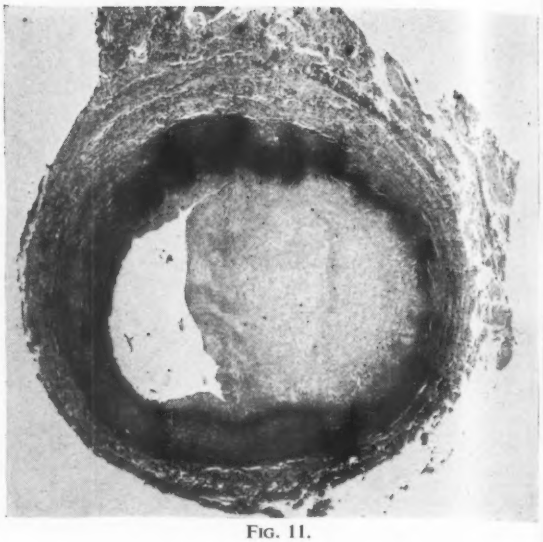

FIG. 11.

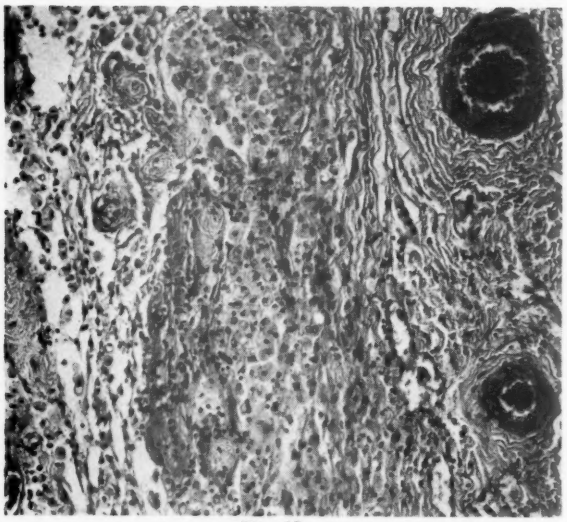

FIG. 12.

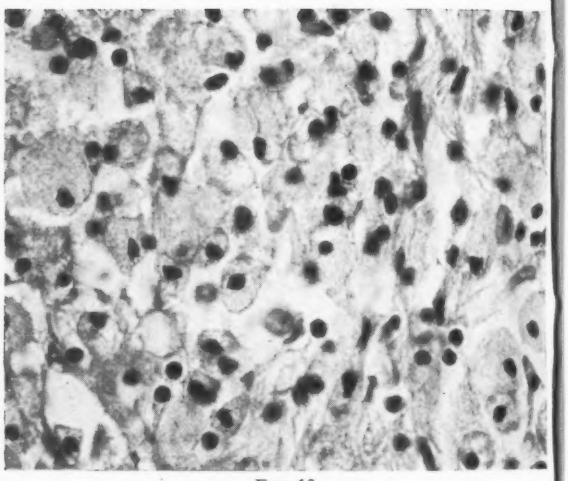

FIG. 13.

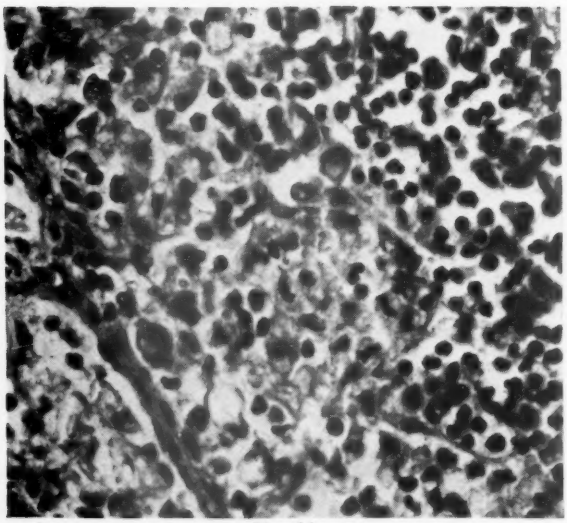

FIG. 14.

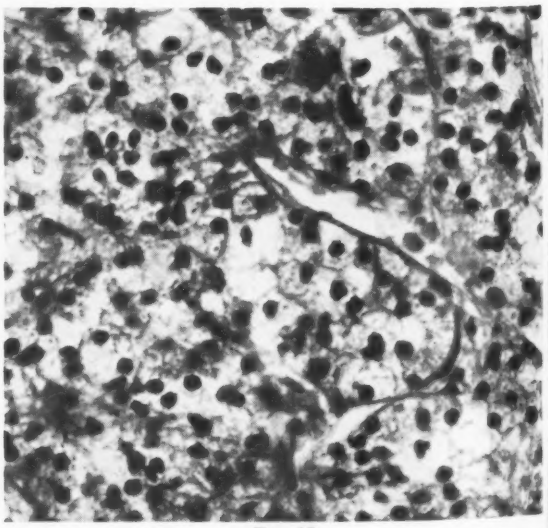

FIG. 15.

Pancreas, Suprarenal and Thyroid Glands. These showed nothing of pathological interest.

Skin. The skin was healthy.

Bones. Sections of a rib and a vertebra showed no abnormality in the bone or marrow. Ossification at the costochondral junction was quite normal.

Bone Marrow. The marrow was active, with normal leucoblastic and erythroblastic elements. Foamy cells were not found.

Attempts to stain the abnormal intracellular and extracellular deposit by Sudan III and Scharlach red, by the osmic acid method, by Nile blue sulphate and by Hoyer's thionin method were unsuccessful.

Specimens of liver and spleen preserved in 10% formalin were examined. The differential lipoid analysis is recorded in Tables 1 and 2.

TABLE 1

DIFFERENTIAL LIPOID ANALYSIS OF LIVER IN CASE 1*

	Dry Tissue (mg./100 mg.)			
	Normal (Age 8 Months)	Case 1 (Age 6 Years)	Normal (Age 6 Years)	Normal Adult
Total fatty acids ..	7·2–8·5	7·4	9·0	8·6–13·0
Phospholipids				
Total	5·4–6·3	4·6	7·8	9·0–11·0
Saponifiable ..	5·4–6·1	4·3	7·8	8·7–10·5
Sphingomyelin ..	·0–0·2	0·3	0	0·3– 0·5
Cholesterol				
Total	0·4–0·6	1·2	0·4	2·1– 2·6
Free	0·3–0·4	1·1	0·4	0·4– 0·6
Ester	0·1–0·2	0·1	0	1·7– 2·0
Neutral fat† ..	3·4–3·9	4·10	3·3	1·2– 4·0
Cerebrosides ..		0·46		0·1– 0·5

* Estimations done by S. J. Thannhauser and R. Holden, Pratt Diagnostic Hospital, Boston, Mass.

† Formula of Thannhauser and Reinstein: neutral fat g.% = g.% total fatty acids minus (g.% cholesterol ester × 0·72 + g.% total phospholipid × 0·69) × 1·04.

TABLE 2

DIFFERENTIAL LIPOID ANALYSIS OF SPLEEN IN CASE 1

	Dry Tissue (mg./100 mg.)			
	Normal (Age 8 Months)	Case 1 (Age 6 Years)	Normal (Age 6 Years)	Normal Adult
Total fatty acids ..	1·2	6·3	5·0	4·0– 6·2
Phospholipids				
Total	3·1	5·1	4·5	5·5–11·0
Saponifiable ..	3·1	4·0	4·1	4·8–10·0
Sphingomyelin ..	0	1·1	0·4	0·7– 1·0
Cholesterol				
Total	0·23	1·8	0·6	0·6– 2·3
Free	0·19	1·7	0·5	0·5– 1·1
Ester	0·05	0·1	0·1	0·2– 1·2
Neutral fat† ..	0·0	2·7	2·8	0·1– 0·0

† Formula of Thannhauser and Reinstein.

Case 2. E.D., a girl, was examined on February 2, 1941, aged 3 years. She died in January, 1944, aged 5 years 8 months.

The father, aged 30 years, and the mother, aged 28 years, appeared healthy, also an elder brother aged 5½ years. There had been a miscarriage at 3 months between the birth of the two children. There was no history of consanguinity or of physical or mental peculiarities on either side of the family.

The antenatal history was apparently normal. The baby was born at the Simpson Maternity Hospital, Edinburgh (No. 9343), at full term. Delivery was spontaneous by vertex presentation. Labour lasted for 10 hours. The infant was slightly shocked at birth, and had two cyanotic attacks on the second day. No abnormality of structure was noted.

She was breast fed for three months (' did not feed as well as brother '). She seemed to thrive in infancy, but the mother noticed that the legs always seemed thin. She noticed kyphosis at 6 months, and a radiograph showed a defect in the dorso-lumbar spine. The first tooth appeared at 16 months. The child first smiled at about 6 months, began to walk round chairs at 2½ years, and to feed herself with a spoon at 2 years. She was still doubly incontinent. Speech was greatly delayed, with no sentence formation. The mother believed she knew the difference between friends and strangers, and between right and wrong. Nasal discharge, first noticed at 10 days old, had persisted ever since, sometimes being more profuse and yellow. The mouth had always been kept open and the tongue projected. The mother first noticed corneal clouding at about 9 months. At 6 months the child began to have (?) epileptiform seizures which usually lasted ' a few minutes '. There were many such ' turns ' in any day for about six weeks, then they ceased. She had bronchitis aged ' a few weeks ', measles at 2 years and left otitis media at 2½ years.

The patient was a typical gargoyle. She was a dwarfed girl (height, 33 in.). The head was large (occipito-frontal circumference, 20¼ in., anterior fontanelle closed). There was a high frontal region, and the occipital ridge was prominent. There was definite bulging of the temporal bones above and behind the ears. The ears appeared low-set and as large as those of an adult. The nose showed a flattish bridge with wide nostrils. The mandible looked rather wide. The tongue lay just inside the lower lip but did not look abnormally large. The teeth were rather widely separated, short, and hypoplastic-looking.

The neck was very short. The trunk also showed numerous abnormalities. The antero-posterior diameter of the thorax was moderately increased. The body of the sternum was abnormally prominent. There was an angular dorso-lumbar kyphosis of moderate degree. The abdomen was moderately enlarged. There were no herniae.

The arms showed limitation of movement at the shoulders, elbows and fingers. When the arms were abducted the scapulae were rotated into the axillae. The elbows could not be quite straightened. There was a permanent semiflexion of all the fingers giving a claw-handed appearance. The legs looked very slender in comparison with the other parts of the body. There was slight limitation of movement in the hips and knees.

Nutrition was satisfactory, and there was a good layer of subcutaneous fat in all areas.

SURFACES. The skin looked healthy and showed good elasticity. The hair was long and flaxen and not unduly fine or coarse. The eyebrows were dark, coarse, and thicker than usual, meeting in the midline. The

complexion was not remarkable. A moderate degree of hypertrichosis was observed on the upper part of the back of the chest and on the back of the upper arms. This hair was fine and fair. The eyes showed slight but definite cloudiness of both corneae. An ophthalmological examination under general anaesthesia was made by Dr. J. R. Paterson and showed a slight but definite degree of papilloedema in both fundi.

MUSCULAR CONDITION. The general muscle volume was below average. The legs were relatively thin, particularly below the knees. The gait was unsteady on walking with assistance. The co-ordination of hand movements was fair.

MENTAL CONDITION. The child was mentally defective. She noticed what was happening around her and looked at one quite knowingly. She became very cross when undressed for examination and resented examination. Said 'Mammy' and occasionally one or two indistinct words accompanied by a movement towards something desired. She tried to help when being dressed and was inclined to be playful.

ALIMENTARY SYSTEM. The abdomen was moderately enlarged. The liver was slightly enlarged, the lower border being palpable two fingerbreadths below the costal margin in the mid-clavicular line. The spleen was not palpable.

RESPIRATORY SYSTEM. There was a slight mucopurulent discharge from both nostrils and a similar post-nasal discharge. There was noisy, snorting breathing. She often stopped breathing for a short time, and this was usually followed by one or two loud snorting expirations. The mother said she had always breathed in this manner.

FIG. 16.—E.D. (Case 2) aged 2 years 4 months. The facies and claw-hand are typical of gargoylism.

X-RAY EXAMINATION OF SKELETON. All of the most characteristic features of gargoylism were present in the skeleton. The sella turcica was enlarged. The ribs were broad. The body of the first lumbar vertebra was small and had a hook-like appearance in the lateral view owing to a defect in the upper half of the anterior part of the body (Fig. 17). The limb bones were thickened and roughly formed, and the smaller long bones showed an abnormal degree of rarefaction and trabeculation. There was severe deformity at the bases of the metacarpals and there was great delay in the appearance of carpal and metacarpal centres of ossification (Fig. 18).

FIG. 17.—Lateral radiograph of dorso-lumbar spine in Case 2, showing typical hook-like deformity of the body of the first lumbar vertebra. The characteristic broad ribs are also found.

FIG. 18.—Radiograph of hand in Case 2, showing a severe degree of malformation of the metacarpal bones and generalized thickening and irregularity.

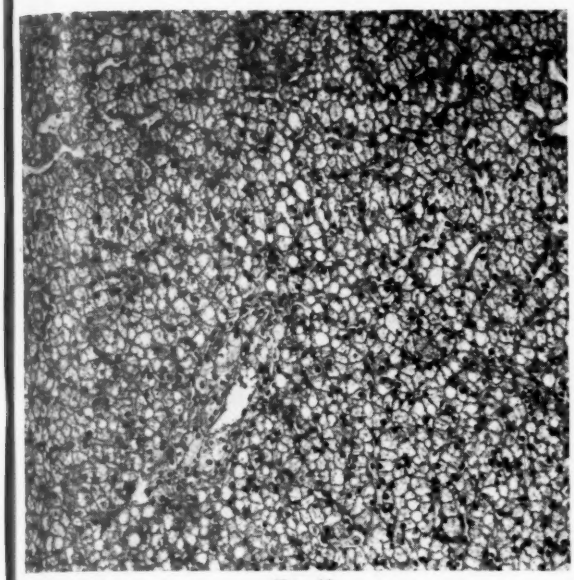

FIG. 19.

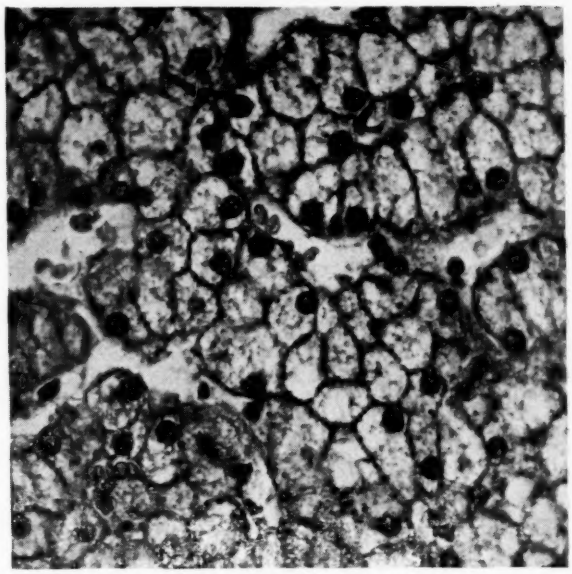

FIG. 20.

When the child was 3 years 9 months (weight, 33¾ lb.; height, 34 in.) the adenoids were removed to try to diminish the chronic nasal discharge.

At 4 years specimens of liver, spleen and tibia were taken for biopsy.

At 5 years 8 months the child died at home. There had been progressive oedema for the last few months which was maximal in the dependent parts, and probably an indication of heart failure.

Histological Report

The following report was made from the biopsy specimens.

Liver (Figs. 19 and 20). The epithelial liver cells were greatly swollen. The cytoplasm contained many vacuoles. The nucleus retained its central position. All zones of the hepatic lobule were equally affected. The sinusoids had been compressed by the swelling of the cells, and were inconspicuous. The Kupffer cells appeared normal and were not vacuolated. The portal tracts and the structures in them were unaltered. Frozen sections stained with Sudan III revealed very little fat in the cells. The material in the vacuoles was not stained by this method.

Spleen (Fig. 21). The sinusoids of the pulp were unusually conspicuous. Their lining endothelial cells were swollen so much that they occupied about half the lumen of the sinusoids; their cytoplasm had a foamy character on account of numerous fine vacuoles. The Malpighian bodies were very large; the lymphocytes appeared normal, but among them there were small groups of large, foamy cells.

Bone. The specimen of tibia examined showed no pathological changes.

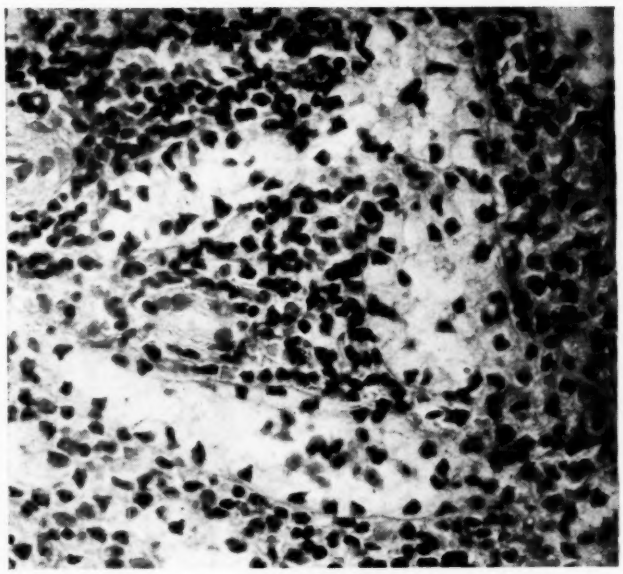

FIG. 21.

FIG. 19.—Liver in Case 2: all the epithelial cells are swollen and vacuolated. The sinusoids have been compressed and are inconspicuous. H. & E. × 100.

FIG. 20.—Liver in Case 2: the epithelial cells are finely vacuolated. The nuclei are neither compressed nor displaced. H. & E. × 400.

FIG. 21.—Spleen in Case 2: the endothelial cells lining the sinusoids are swollen and vacuolated, and cause the sinusoids to be unusually clearly defined. H. & E. × 400.

Case 3. L.D., a girl, was the sister of E.D. (Case 2). She was examined on March 24, 1950, aged 2 years 4 months.

The family history is described under Case 2. After the death of E.D. (Case 2) a fourth pregnancy resulted in a stillborn infant, a fifth in the birth of this child, and a sixth in the birth of a male infant now aged 10 months and quite normal.

The baby was born at full term by breech delivery after a normal pregnancy (birth weight, 7½ lb.) at the Western General Hospital, Edinburgh. Nothing abnormal was observed in the neonatal period. She was breast fed for three months.

Development is retarded, and she cannot yet assume a sitting position by herself. She began to walk around objects at 1 year 8 months, but still falls readily. Speech began at 2 years, but is still poor. She still has urinary incontinence. She has never had any fits.

At 7 months a lump began to grow on the top of the head.

Her appearance (Fig. 22) is typical of gargoylism. (height, 33 in.; weight, 31 lb.; head circumference, 19 in.). The cranium is long and narrow, with a low, narrow forehead. A large, oval, bony prominence in the region of the anterior fontanelle is seen; also bony swellings behind and above the ears. The occipital ridges are prominent, the nose bridge depressed and wide. The eyes are slightly protuberant and corneae slightly opaque, the eyebrows thick, the mouth a little large, and the tongue large but not fissured. The cheeks are ruddy.

There is pronounced dorso-lumbar kyphosis, a protuberant abdomen, but no umbilical hernia. The limbs look short and there is genu valgum. Extension is limited at the shoulders, elbows and fingers, and to some extent in the legs. There are moderate claw-hands with incurving little fingers.

A systolic murmur is heard in all areas of the heart.

The liver is enlarged to three fingerbreadths below the costal margin in the mid-clavicular line. The spleen is moderately enlarged and easily palpable.

She is a mentally defective child of moderate degree. The eyes show a vertical nystagmus, more on the right than on the left, particularly when looking at an object. No other abnormal nervous signs were found.

There is a continuous mucopurulent rhinorrhoea and post-nasal discharge. The chest is normal.

Urine and blood examination were normal.

X-ray examination of the skeleton showed the typical features of gargoylism (Figs. 23 and 24), also the peculiar osseous swelling in the region of the anterior fontanelle observed clinically (Figs. 25 and 26).

Histological Report

Liver (Figs. 27 and 28). Frozen sections of a biopsy specimen were examined for glycogen and fat, also paraffin sections.

In the routine haematoxylin and eosin sections the liver cells appeared swollen and vacuolated. Most of the vacuoles were small, but some filled most of the cell. The nucleus was sometimes central, but often lay to one side of the cell; it retained its round shape and was never flattened. The sinuses were compressed and narrow and the tissue appeared bloodless. The Kupffer cells were not swollen. The portal tracts showed no increase of fibrous tissue, but they were conspicuous on account of cellular infiltration. The cells were lymphocytes and histiocytes, and among the latter some were immensely swollen and foamy. In the small portal tracts there were only two or three cells in this condition, but in some of the larger ones the foamy cells were quite conspicuous.

In the frozen sections stained for fat by the Scharlach red method, stained fat was present in excess in some of the liver cells, but was far from accounting for all the vacuolation. It was not detectable in the foamy histiocytes in the portal tracts. In sections stained for glycogen, only a small quantity was present; the majority of the cells contained none.

The histological features were typical of the liver in gargoylism. The stored substance failed to stain by ordinary methods for either fat or glycogen.

FIG. 22.—L.D. (Case 3) aged 2 years 4 months. The appearance is typical of gargoylism, particularly the facies. Note also the claw-hand.

Biochemistry

A biopsy specimen of liver was submitted to Dr. S. L. Thompsett. The results are shown in Table 3.

TABLE 3

BIOCHEMICAL ANALYSIS OF BIOPSY SPECIMEN OF LIVER IN CASE 3

	Dry Tissue (mg./100 mg.)*			
	Normal (Age 8 Months)	Case 3 (Age 2 Years 8 Months)	Normal (Age 6 Years)	Normal Adult
Total fatty acids ..	7·2–8·5	8·0	9·0	8·6–13·0
Cholesterol	0·4–0·6	1·0	0·4	2·1– 2·6
Glycogen		13·3		4·4–25·2†

* Estimations were done on fresh tissue. Figures for dry tissue calculated on the assumption that wet tissue contains 75% of water.

† Range of glycogen content in fresh biopsy specimens of liver from 10 adults with normal livers (MacIntyre, Pedersen and Maddock: 1941). In glycogen storage disease the liver contains 40 mg. or more per 100 mg. of dry tissue.

FIG. 23.—Lateral radiograph of dorso-lumbar spine in Case 3, showing the characteristic defect of the anterior part of the body of the lower dorsal and upper lumbar vertebrae.

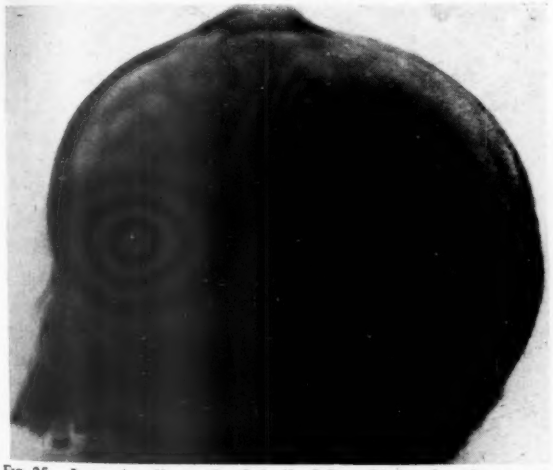

FIG. 25.—Lateral radiograph of skull of Case 3, showing the osseous swelling in the region of the anterior fontanelle. The deep convolutional markings indicate a long-standing increase of intracranial pressure.

FIG. 26.—Antero-posterior radiograph of skull of Case 3.

FIG. 24.—Radiograph of hand of Case 3, showing characteristic malformation of the metacarpal bones.

THE LITERATURE ON THE PATHOLOGY OF GARGOYLISM

The pathology in each individual organ will be reviewed, and the local features will then be linked together by a discussion of the general pathological features of the disease. The incompleteness of most of the case reports precludes an accurate assessment of the incidence of characteristic lesions of the disease in most of the organs of the body.

The Liver

Morbid Anatomy. This was described in 23 cases, though often briefly. The organ was enlarged in 16, of normal size in four, small in one, and the size was not mentioned in two. The anterior border was rounded in a few of the cases with enlargement. Abnormal pallor was described in the majority, particularly of the cut surface. It was described as soft in four cases and firm in four cases. Two of the firm livers had distinct lobular markings suggestive of cirrhosis.

Histology. Microscopic examination was done in 24 cases, including six biopsy specimens. The parenchymal cells were enlarged and contained vesicular or foamy cytoplasm in a high proportion of cases; an eccentric nucleus was noted in several instances, also a disturbance of the normal cord arrangement of the cells. Increased connective

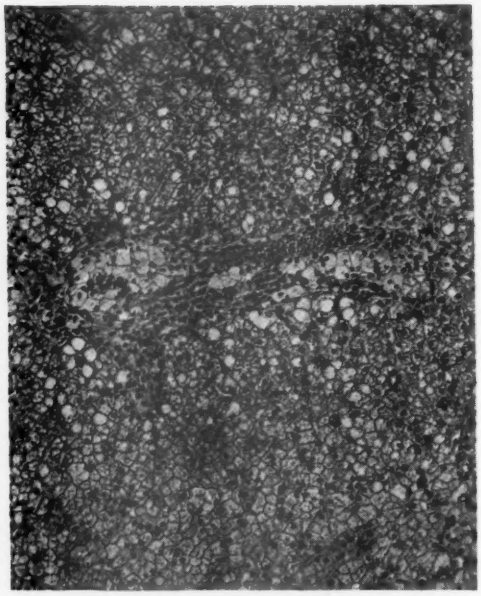

FIG. 27.—Liver of Case 3: the cells are swollen and contain fine vacuoles in the cytoplasm; some have larger vacuoles. A group of 'foamy' histiocytes lies in a portal tract in the centre of the field. H. & E. ×85.

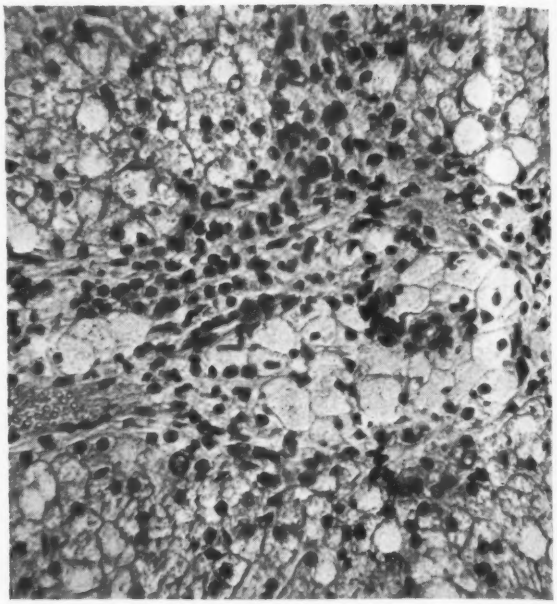

FIG. 28.—Liver of Case 3: higher magnification of part of field shown in Fig. 27. Note detail of vacuolated liver cells, and 'foamy' histiocytes in a portal tract. H. & E. ×250.

tissue in the portal spaces, causing the hepatic lobules to be more distinctly outlined than normally, was observed in several cases, and in three instances irregular strands of hyaline connective tissue were observed throughout the parenchyma.

The Kupffer cells showed vesiculation resembling that seen in the parenchymal cells in five cases. No histological abnormality was detected in the liver in three cases.

The Spleen

Morbid Anatomy. The spleen was described in 21 cases, briefly in most of them. It was enlarged in 15, usually moderately, and normal in size in six. In some the cut surface looked normal, in others the Malpighian bodies were not visible. A few were 'pale'. The consistence was seldom mentioned and was therefore presumably normal, as a rule, but it was described as firm in three cases and soft in two.

Histology. Microscopy was done in 17 cases, two of the specimens having been obtained by biopsy. The lymphoid follicles were described as widely spaced and small in a minority of the cases. The most striking abnormality, observed in most instances, was enlargement of the reticulo-endothelial cells lining the sinusoids and the presence of many large mononuclear cells in the intersinusoidal spaces; both types of cell were distended and vacuolated. Enlargement and vesiculation was seen in some of the lymphoid cells in the Malpighian bodies in two cases. The pulp was described as normal in five cases.

The Heart

Morbid Anatomy. The heart was described in 21 cases. It was enlarged in the majority. Hypertrophy of the left ventricle was a notable feature, as a rule. The pericardium had a normal appearance in all cases, but the epicardium showed areas of opaque thickening over the ventricles in three instances. The myocardium looked normal in all cases except two in which it was pale. The endocardium had a normal appearance in most of the specimens but in six it was thickened and opaque: in one case this change was apparently generalized, in another it was limited to the left auricle, in two to the left ventricle, and in one to both ventricles. The coronary arteries were described as abnormal in three cases, including our Case 1: the main vessels on the surface of the heart showed conspicuous, rigid, nodular white cords caused by extreme thickening.

The most constant abnormality in the heart was in the valves, particularly the mitral valve, and in the chordae tendineae of affected atrio-ventricular valves. One or more abnormal valves were described in 14 of the 20 cases. The mitral

valve was affected in all of the 13 cases in which the various valves were specified, the tricuspid valve in eight, the aortic in seven and the pulmonary in two. There were only two cases in which all the valves were affected. In most cases the affected mitral and tricuspid valves were thickened and opaque, though in some this was not so: thickening was not accompanied by shrinkage in the few cases in which this aspect was mentioned; Kressler and Aegerter (1938) observed some deposition of calcium in the thickened mitral valve. In the majority of cases the mitral valve showed numerous small fibrous nodules along the free edge and line of closure of the cusps; these were sometimes discrete and sometimes had coalesced. Nodules were found in a few cases in which the cusps were said not to look thickened. In our case and that of Strauss (1948) there were fibrous nodules at the attachment of the chordae to the cusps. The chordae of affected mitral and tricuspid valves were thickened and shortened in varying proportion and degree.

Affected aortic and pulmonary valves were described as thickened; in two cases this was said to be more pronounced at the free edges. In one case there was a deposit of calcium at the base of an affected aortic cusp.

Histology. Heart tissues were examined microscopically in 16 cases. The pericardium was mentioned in eight instances. It looked normal in two cases and thickened in two. In three cases there was a slight lymphocytic infiltration, while in two, swollen mononuclear cells of the type seen in other tissues were observed, particularly in the vicinity of blood vessels. The epicardium was examined in two cases in which its naked-eye appearance was normal, and it did not show any abnormality.

The myocardium was mentioned in 12 cases and vacuolation of the fibres was a feature in eight instances, two of which also showed brown atrophy; in one case vacuolation of muscle fibres was a notable feature in the auricles but none was seen in the myocardium of the ventricles. Groups of muscle fibres were replaced by delicate connective tissue with vacuolated cells in three cases, this change being adjacent to the abnormal valvular endocardium in one of these. The interstitial tissue of the myocardium was mentioned in four cases: the fibrous tissue was increased in amount and the connective tissue cells were swollen and vacuolated in three instances; in two cases small lymphocytic collections were found in a few places.

The mural endocardium was normal in two cases and thickened in six, with changes similar to those to be described in the valves. The endocardium over a papillary muscle in one case and in the vicinity of a valve in another showed similar changes.

The abnormal valves and the endocardium of abnormal chordae tendineae were thickened and consisted of an increase of fibrous tissue in various stages of development with swollen vesicular connective tissue cells between the collagenous fibres; the number of these cells was usually inversely proportional to the amount and density of the fibrous tissue. In three cases with less advanced fibrosis the cells were arranged in columns and the tissue had the ' appearance of fibrocartilage '. With the exception of one case no vascularization was seen; inflammatory cells were not found. Degenerate foci in the valves, with calcification, were seen in four cases.

The coronary arteries were thickened in five cases.

The Blood Vessels

Morbid Anatomy. Certain of the blood vessels were described in 12 cases. No abnormality was observed in two of these.

The naked-eye appearance of the aorta was mentioned in 11 cases and it was abnormal in eight: several small, pale yellow intimal plaques were observed just distal to the aortic valve in five cases; in one case similar lesions were found in the descending aorta, particularly near the openings of the intercostal vessels; the lesions were ' longitudinal ' in two cases. The large branches of the aorta were similarly affected in one case.

The coronary arteries were described in seven cases and gross changes were observed in three of them, one being our Case 1. They looked normal in the other four cases. In our case ' the thickened condition of the coronary arteries was most arresting. They were straight, prominent and hard. They felt like nodular cords and were studded with numerous small, pale yellow flecks. Not only the main branches but even the smallest visible twigs on the surface of the heart were affected in this way.' Lindsay *et al.* (1948) in two of their cases (Nos. V and VII) found ' all the main coronary arteries extremely thickened due to the deposition of greyish translucent material within the intimal layer. This process left a small cleft-like lumen in these vessels.'

The surface cerebral arteries were mentioned in four cases. They looked normal in two over the cortex and in one at the base of the brain, but in our Case 1 the arteries at the base of the brain showed white flecks in their walls resembling atheromatous deposits. In four cases the cerebral white matter showed many tiny perivascular

cystic spaces ½-1 mm. in diameter. They contained ' pale translucent mucoid material '.

The pulmonary vessels appeared normal in two cases, but the large branches showed slight thickening in one.

In one case a main pancreatic artery showed mild eccentric thickening of the intima.

Histology. Histological descriptions of some vessels were given in 14 cases. In 13 cases the vessels examined were specified and were as follows:

ABNORMAL. Aorta eight, main coronary seven, brain five, spleen three, pancreas three, kidney two, pulmonary one, carotid one, mesenteric one, radial artery one, anterior tibial artery one.

NORMAL. Basilar two, hepatic two, and each of the following one, small coronary, axillary, internal carotid, vertebral, renal, lingual and choroid plexus.

In the aorta the localized zones of intimal thickening had the same features as in other arteries, namely connective tissue fibres with cleft-like spaces and swollen vesicular connective tissue cells. The media in the affected areas showed unusually distinct elastic fibres separated by fusiform clefts containing swollen connective tissue cells. In some cases the adventitia was said to show similar changes and in others to be normal.

The histological features in the medium-sized arteries listed above were fairly uniform, and the description given in our Case 1 is representative. The coronary arteries on the surface of the heart showed striking changes. The intima was immensely thickened in an almost uniform concentric manner. It was composed of fibrous tissue in the interstices of which were numerous large foamy cells. The surface endothelium was intact. The internal elastic lamina could be traced round most of the circumference but had suffered fragmentation at a few points. The media was stretched and thin and had been slightly invaded by foamy cells, especially in the inner part, immediately external to the elastic lamina, but here and there also in the outer part. In some of the other arteries, such as the radial and anterior tibial in our case, the changes which were essentially the same differed in two respects: the intimal thickening was not concentric, but more on one side than the other, and the abnormal tissue that was responsible for it was more densely fibrous and contained fewer foamy cells.

The cerebral vessels in the white matter showed a great widening of the adventitia with wide spaces which contained irregular fragmented collagenous fibres, a variable number of distended connective tissue cells and in some cases a deposit of extracellular amorphous material, hence the small cysts observed macroscopically when these changes are extreme.

In one case a large renal artery at the junction of cortex and medulla showed interesting changes, since this is the only record of the muscle fibres of the media showing vacuolation; they were extremely vacuolated and had small pyknotic nuclei. The internal elastic membrane was distinct. The other layers of the vessel were normal. In another case a large intrarenal artery showed focal intimal thickening.

The Meninges

Morbid Anatomy. Reference was made to the meninges in 11 cases. Gross pathological changes were found in three cases, the seventh case of Lindsay *et al.* (1948), Magee's (1950) case, and our Case 1. In the first of these the superior and anterior surfaces of both cerebral hemispheres were covered with encapsulated collections of dark brown, viscous, sanguineous fluid which had no doubt exuded from subdural haematomata. Elsewhere the subdural space was lined with thick, yellowish-green fibrin indicating recent meningitis. No gross subarachnoid exudate was seen.

In Magee's case the dura mater looked normal, and had a smooth, glistening inner surface, but the pia arachnoid covering the convexity of the left cerebral hemisphere was either enormously thickened, or adherent to a smooth, opaque, grayish covering of firm tissue which measured 0·5 cm. or more in thickness in some places. This densely organized tissue completely obscured the convolutional pattern. There was a similar, though thinner, layer over the right frontal lobe, and a large encapsulated subdural haematoma covered most of the right hemisphere.

Our case showed ' adhesions between the dura mater and the pia arachnoid over the vertex of the brain. Over this area there was a deposit of yellowish material which adhered to the inner surface of the dura and to the arachnoid. The leptomeninges showed a peculiar greyish opacity which intensified to whiteness over the temporal poles. The subarachnoid space was slightly enlarged and contained a quantity of gelatinous material '.

Minimal data are given about the other eight cases which showed some abnormality. In five cases the leptomeninges showed local or diffuse thickening with a varying degree of opacity. In one ' the dura was considerably thickened ' and in another ' the dura was adherent to the anterior part of the left frontal lobe '. In one case ' the

meninges, especially over the frontal lobes, were thickened and greyish '.

Histology. Some microscopical data are given in eight cases. In the seventh case of Lindsay *et al.* (1948) the microscopic changes were consistent with the changes produced by subdural haematomata and meningitis.

Microscopically the thick, firm tissue in Magee's case was seen to be composed mainly of thick, dense, collagenous connective tissue which resembled dura mater. The arachnoid could not be distinguished, but there was a clear line of cleavage between the leptomeninges and the surface of the cerebral cortex. Large numbers of elongated 'macrophage' cells with small, darkly staining nuclei and abundant, lightly staining reticulated cytoplasm lay between the strands of coarse connective tissue. The cytoplasm was honeycombed with small, round, non-staining vacuoles. Nearer the surface of the cortex there were irregular sheets of cells with large, densely staining, pleomorphic nuclei and abundant honeycombed cytoplasm; these cells had a more rounded, fuller appearance than those lying in the interstices of the denser collagen fibres. In some places the cells were so closely packed that large masses of them were contiguous. Fine strands of connective tissue ran into these densely cellular areas. By means of a variety of staining methods they concluded that the major portion of the substance in the distended cells was a neutral fat, but that 'the consistent failure to stain all the cytoplasm leaves doubt about the nature of the unstained portion'.

In our case 'the deposit on the inner surface of the dura mater was composed of sheets of foamy cells with a small amount of supporting fibrous tissue and blood vessels. In the subarachnoid space there were moderately numerous histiocytes, and distension of the subarachnoid meshes by extra-cellular amorphous material was a striking feature' (Figs. 12 and 13).

Tuthill (1934) found 'a universal distribution of lipoid particles in conglomerate masses in the thickened meninges, particularly at the base of the brain'. She believed that these changes could have been caused by the associated tuberculous meningitis. In one case the arachnoid showed 'fibrous thickening and oedema', in another 'some of the connective tissue cells showed typical enlargement', while in another 'the subarachnoid space was wide and contained an increase of collagenous fibres and the fibroblasts were swollen and vesicular'. In Green's (1948) case the leptomeninges over the brain and spinal cord were thickened and contained scattered compound granular cells intermingled with large macrophages.

The Brain

Morbid Anatomy. The macroscopic appearance of the brain was mentioned in 22 cases, sometimes only briefly. The brain was enlarged in 11 of 17 cases in which size was mentioned. Symmetrical internal hydrocephalus was a feature in nine cases. The convolutions were flattened in three cases, in one of which the brain looked swollen and oedematous; in two cases they showed some atrophy. Small perivascular cysts containing mucoid material were observed in the white matter on sectioning the brain in five cases; this feature was revealed in even more cases on microscopy. In two cases, including Case 1, a moderate degree of atrophy of the white matter was found. In one case the cortical layers of the cerebral hemispheres were widened and had an unusual grey, translucent appearance; scattered throughout this layer were numerous small, yellow, opaque zones of softening. In another case the cortical layers of the cerebral hemisphere were less distinctly outlined than normally, and were apparently separated into an outer and an inner cortical layer. Green (1948) reported moderate reduction in the grey matter of the cerebral hemispheres and increased consistency of the white matter.

Ependymal changes were observed in two cases. In one case it appeared thickened in the lateral ventricles and had minimal brownish pigmentation. In the other, in the same situation, it was oedematous, congested and opaque and covered in part with a fibrinous exudate.

Histology. Microscopy was done in 20 cases. The most detailed reports of the histology of the central nervous system were given by Tuthill (1934), Ashby *et al.* (1937) (Case 1) and Green (1948). Pathological changes were found in the brain in all cases except two, the mentally defective patient of De Lange *et al.* (1944), who was regarded as a *forme fruste* of gargoylism, and the 4½-months-old infant recently described by Lindsay (1950). In both cases the central nervous system was found to be completely normal on careful examination of all portions.

Abnormal cortical cytoarchitecture was described in seven cases. This was usually described as 'irregularity of nerve cell layers'. Ashby *et al.* in their first case described 'a loss of the normal columnar arrangement of the nerve cells'. Tuthill found disturbed cell arrangement only in the temporal lobes near the cornu ammonis. Reduction of the cortical nerve cell population was mentioned

in four cases, but may well have occurred in some others.

In 16 of the 18 cases showing pathological changes in the brain the cortical nerve cells were affected. In one of the remaining two cases they were 'not enlarged' and in the other they were not mentioned. The following is a typical description of the cortical cells: 'The majority of the cortical cells are swollen, rounded or oval, and are interspersed with normal and disintegrating cells. The nuclei are usually displaced eccentrically and in some cells are degenerate or absent. The cytoplasm consists of greyish, granular non-staining material; it is sometimes vesicular, and contains either no or a greatly diminished amount of Nissl substance'. Little was said about the cell processes in most of the cases. In several of their cases Lindsay *et al.* made the rather vague and sweeping statement that 'the cell processes had usually disappeared'. Some other authors gave a more detailed description: the dendrites were described as 'nowhere conspicuous' by Ashby *et al.* in their first case, 'slightly puffy' by Tuthill and 'wide and distended' by Kressler and Aegerter (1938). The axons showed less abnormality than the dendrites: Ashby *et al.* in their first case described them as normal and in their second as 'relatively well preserved'; Tuthill found them 'slightly puffy' and Kressler and Aegerter 'wide and distended'.

The nerve cells were not equally affected in all parts of the central nervous system, though as a rule some abnormal cells were found everywhere. The distribution of the more severely affected cells varied considerably from case to case though in a majority certain areas showed a predilection for the optimal changes. In 14 cases in which the distribution of pronounced cell changes was mentioned, the cortex was specified in 11; in some instances certain areas of the cortex were more severely affected than others. The basal nuclei showed optimal nerve cell changes in nine cases; the various nuclei were not specified, as a rule, but when they were, some, such as the optic thalamus, were usually more affected than others. Certain nuclei of the brain stem showed pronounced cell changes in 10 cases. The cerebellum was usually less severely affected than the cerebrum, but it also showed pronounced changes in seven cases; the Purkinje cells in four cases, the external granular layer in two cases, and the dentate nucleus in one. Severe changes were observed in the anterior horn cells of the spinal cord in six cases; two of these also showed similar changes in the posterior horn cells. Minimal cell changes were described in the cortex in two cases, in certain of the brain stem nuclei such as the hypoglossal in four, and in the cerebellum, particularly in the Purkinje cells, in three. The ganglion cells in the anterior horn of the spinal cord showed minimal changes in one case and moderate in one case, in addition to the five cases showing severe changes.

The myelin sheaths of the nerve fibres were referred to in eight cases. No demyelination was observed in three cases, but it was present in five instances. Tuthill found universal thinning of the myelin sheaths in the white substance of the cerebral hemispheres, and typical fat granules in a few large areas which showed destruction of myelin sheaths; the optic nerves showed an entire loss of myelin with a heavy mantle of fat granule cells. In one of their cases Lindsay *et al.* found 'the fibre pattern unusually rarefied with little myelin substance present in the fibre tracts', while in another 'there was mild demyelination in the anterolateral columns of the spinal cord'. Green (1948) reported minimal demyelination in the cortical white matter and in the basal ganglia. Jervis (1950) found large areas of active demyelination frequently in the white matter.

Gliosis was referred to in only a few cases. Ashby *et al.* found several zones of pronounced gliosis in the basal ganglia in both of their cases. Lindsay *et al.* described an excess of glial and microglial cells in the cortical white matter of their case which showed some demyelination in that situation. In another case of the latter authors the glial cells in the cortex showed changes resembling those seen in the nerve cells, but they were less severe. Green reported considerable glial proliferation in the grey and white matter of the cortex, in the basal ganglia and spinal cord, and minimal proliferation in the brain stem and cerebellum. He also observed distension of cell bodies of some glial cells. Jervis observed considerable neuroglial reaction in the cortex in one of his cases. Lindsay *et al.* observed that the astrocytes and oligodendrocytes in the cortical and subcortical layers in one of their cases had abundant, clear, vacuolated cytoplasm similar to that seen in the nerve cells.

Sympathetic ganglia were examined in three cases (Magee, 1950; Jervis, 1950) and, in all, the neurons showed changes similar to those described in the neurons of the central nervous system.

A greatly widened adventitial coat and very wide perivascular spaces surrounded the medium-sized and smallish vessels of the cerebrum in all cases in which the cerebral vessels were mentioned. The histological appearance has been described in the section on blood vessels.

A deposit of variable amount was found in the nerve cells in all parts of the central nervous

system. Ashby *et al.* showed that the granular deposit in the nerve cells seldom failed to be revealed in cells even of normal contour and size. It was, however, most abundant perivascularly, the largest amount in this situation being seen in the globus pallidus and in the following regions in diminishing amounts: putamen, caudate nucleus, optic thalamus, zona reticulata of the substantia nigra and dentate nucleus. In the cerebral cortex it was found around the blood vessels only in the pre- and post-central zones. A small amount of deposit was also found in the grey matter of the cerebellar hemispheres where, in one or two situations, it lay free between folds of pia mater covering the folia. None was found in the white matter of the cerebrum or cerebellum. In their second case Ashby *et al.* found small amounts of deposit in the nerve cells, but it was insufficient to cause either ballooning of the cell body or displacement of the nucleus except in one or two regions. No free lipoid could be identified with polarized light in this case; a very detailed examination of the deposit was not made because of the age of the material. Tuthill found that all of the nerve cells contained 'lipoid' regardless of the degree of morphological change, and the amount varied with the degree of swelling; in common with others he found perivascular 'lipoid' infiltration of the medium and smaller sized cerebral vessels; unlike others he found 'lipoid'-containing cells scattered throughout the white matter. Kressler and Aegerter merely stated 'about the nuclei of many of the nerve cells were clear, crescent-shaped areas which contained considerable quantities of lipoid material'. In our case the nerve cells in all parts examined showed granules of an isotropic substance in the cytoplasm; histiocytes containing 'lipoid' were present in the perivascular spaces; in the cerebral white matter especially this was associated with distension of the adventitia of the blood vessels with extracellular 'lipoid'.

Eyes

Morbid Anatomy. Reports on the eyes are available in 10 cases, in six of which the eyes were examined post-mortem by ophthalmologists. The reports in the latter cases will be considered, because they are the more authoritative. They were published by Berliner (1939), Rochat (1942) and Zeeman (1942), each one case, and by Cordes and Hogan (1942) three cases. The latter authors state that corneal clouding is present in over 75% of cases, generally appears before the age of 3 years, and has been observed at birth. Apart from the ground-glass appearance and diffuse haziness there is no sign of inflammation in the eye or of vascularization of the cornea. On examination with the slit lamp the haze is resolved into uniformly distributed, tiny, grey or yellow-grey dots which at first occupy the middle and deeper layers of the cornea. Later they are distributed throughout the stroma. These dots do not appear to be crystalline and are only slightly refractile. After a certain degree of opacity is reached the cornea remains unaffected. Hyaline or calcareous degeneration of this material in the cornea has not been reported.

Histology. Microscopy was done in 11 cases, six being reported by ophthalmologists. The reports of the ophthalmologists were in agreement. In all cases pathological changes were limited to the cornea where they were concentrated in or near Bowman's membrane. In this membrane numerous defects were scattered across the whole cornea, and these were occupied by large cells containing vacuolated cytoplasm, the cells varying from spindle-shaped to globular. Their cytoplasm contained numerous glistening granules which were sometimes confluent and looked like snowflakes. They were soluble in ether and alcohol but were not doubly refractile in polarized light. Reactions with fat stains such as osmic acid and Sudan III were negative. Sometimes two corneal lamellae were separated and the resulting space was filled with large granular cells of the same type. Scattered swollen corneal corpuscles containing granules were also observed. Cordes and Hogan pointed out that both normal tissue cells and phagocytes are therefore involved. These authors concluded that the numerous corneal opacities, seen as tiny dots with the slit lamp, are produced by the infiltration of phagocytic cells into the region of Bowman's membrane causing thinning and ruptures in it by the swelling of these corneal corpuscles. There was no other cellular or fluid extravasation into the stroma to account for them.

Lindsay *et al.* in their seventh case described changes in the eyes additional to the characteristic changes in the cornea. The epithelial cells on the surface of the ciliary body and the posterior surface of the iris were enlarged and vacuolated. The connective tissue of the iris, ciliary body and choroid was loosely arranged and contained numerous vacuolated macrophages. Many of the nerve cells in the nuclear layer of the retina were enlarged and vacuolated.

Bone and Cartilage

Morbid Anatomy. The skeletal malformations are too well known to need recapitulation.

Histology. Reports on bone and/or cartilage

have been given in 20 cases. The specimens were obtained by biopsy in several instances. There were eight individual reports before Lindsay and his colleagues described the histology of certain bones in eight of their cases. In the earlier cases the bones, which were cartilage bones taken from a variety of situations, were described as normal in three cases, and as showing hypoplastic chondrodystrophy in two cases. In three cases, however, swelling and vacuolation of cartilage cells was observed: Schmidt (1942) was the first to report this feature. No abnormality was seen in the bone examined in our two cases, or in the costal cartilage in the two cases recently reported by Jervis (1950). More extensive examination would probably have revealed some abnormality in those cases in which none was found in the single specimen examined, since abnormal morbid anatomy of the bones is almost a constant feature of the disease.

Lindsay *et al.* demonstrated fairly uniform changes in each of the eight cases in which the bones were examined. The most striking feature was swelling and vesiculation of cartilage cells, though several other characteristic changes were observed. The costochondral junctions were examined in several cases, and in all of them the cartilage cells were unusually large and almost completely filled the lacunar spaces in the cartilaginous matrix. The cytoplasm of the cartilage cells was more abundant than usual and was granular and vesicular. The osteocytes were similarly affected as a rule. Some of the connective tissue cells in the outer layer of the periosteum also showed similar changes and the periosteum was usually thickened. In some cases there was no distinct epiphyseal line with little evidence of growth. In all cases the cortical layer of rib was thin and usually irregular also. Abnormal lumbar vertebrae were examined in two of the cases of Lindsay *et al.* The epiphyseal lines were extremely irregular, and all the cartilage cells both of hyaline cartilage, and of fibrocartilage in the intervertebral discs, as well as the osteocytes and periosteal connective tissue, showed distension of cytoplasm by granular, grey material. The bony trabeculae of the vertebral bodies were thin and irregular and showed no osteoblastic activity. Anteriorly at the point of the characteristic indentation the cartilage was deficient and was replaced by dense fibrous tissue; it appeared as though the vertebral body had collapsed anteriorly because of the unusually thin layer of cortical bone forming the anterior portion of the vertebral body.

Strauss (1948) gave a detailed account of the histology of a rib and an abnormal lumbar vertebra in her case. In a rib

'the resting cartilage of the epiphysis was normal. The zone of proliferating cartilage was shortened and the cartilage columns were plump, and in places missing. Where the proliferating cartilage cells were absent there was an area of vascular connective tissue containing many large, swollen, vacuolated cells similar to those seen elsewhere in the connective tissues. This area lay approximately in the centre of the epiphyseal zone, close to the costochondral junction. At its base there was a thin, transversely disposed layer of newly-formed bone which lacked a calcified cartilage ground substance, in contrast to bony trabeculae normally formed from the cartilage. The cancellous portion of the rib showed normal trabeculae. In the periosteum and perichondrium the collagen fibres appeared separated by large numbers of vacuolated, spindle-shaped cells having small eccentric nuclei. The periosteum was markedly thickened by the presence of the large cells and a conspicuous increase in the number of collagen fibres. The infiltrated periosteal tissue appeared to be engaged in the resorption and reconstruction of cortical bone which, along the surface of contact, showed many shallow and deep lacunae filled with the swollen cells. Occasionally, small fragments of newly-formed bone were completely embedded in the infiltrated periosteal tissue, and the osteocytes still resembled the swollen periosteal cells. It thus appears that bone may be formed directly within this tissue. The cortex itself was thick. The endosteum was thin and delicate, and there were very few osteoblasts and osteoclasts. The perichondrium also showed infiltration with large cells. These appeared to become incorporated in the cartilage, which was more cellular in its peripheral portions than in its depth. Also, the cartilage cells there appeared somewhat larger, but otherwise were not remarkable. One of the ribs showed a circular periosteal band interposed between the epiphyseal cartilage and the metaphysis, thus producing a marked constriction of the epiphyseal zone. The peripheral parts of the shaft were formed directly from the periosteal band instead of from cartilage. The same foam cells present elsewhere in the periosteum were scattered throughout the periosteal wedge, which otherwise was formed by dense collagen fibres. A sagittal section of the lumbar vertebra showed the structure of the spongiosa to be normal. The marrow was cellular and there were few fat cells. Proliferating cartilage was very scanty; columns of cartilage either were missing or very short. Thus, much of the cartilage which would normally proliferate had remained in the resting stage. Penetration of marrow cavities into the cartilage was very slight and occurred only where the short columns were present, in the centre of the epiphyseal line. The zone of provisional calcification was almost absent, and bone was laid down directly at the border of the epiphyseal cartilage, as a transverse layer. Accordingly ossification was mainly perichondral. The longitudinally directed trabeculae seen in normal bone were rare. The deep concave groove along the anterior border of the vertebra was filled with thick collagen fibres forming interlacing bundles. Adjacent to the cortex there was a layer of vacuolated cells which appeared to penetrate into the cortical bone, giving it an eroded border. Very few osteoclasts were seen, but the vacuolated

cells appeared to exert osteoclastic activity. Small fragments of bone were laid down in the infiltrated zone of the periosteum. Another lumbar vertebra showed a marked overgrowth of cartilage along its anterior border. Apparently this was the result of the poor endochondral bone formation from the epiphyseal cartilage. Thus the spongiosa of the vertebra became disproportionately small and its outline deformed. The anterior border of the vertebra became shorter than the posterior border and much more concave. The concavity was filled with periosteal and perichondral tissue consisting of interlacing fibres which blended with the overhanging cartilage, and of numerous vacuolated cells which appeared to become incorporated in the cartilage.'

Similar changes were seen in various other bones. In three cases the skull did not show any separation into inner and outer tables. The bronchial cartilages were examined in four cases and the tracheal cartilages in three; changes similar to those seen in epiphyseal cartilages were the rule.

The Kidneys

Morbid Anatomy. The gross appearance was described in 14 cases. There was no abnormality of size. The capsule appeared thickened in only one case but stripped easily in all. Cortico-medullary differentiation was diminished in only one case. The cut surfaces of the cortex and medulla were noticed to be pale in three cases and the cortex in another two.

Histology. Microscopy was done in 14 cases. No abnormality was observed in five.

Two cases showed evidence of deposition of an abnormal substance. There was distension and vacuolation of certain cell elements in one of these cases, and a deposition of a non-staining granular material in certain cells and interstitial tissues in the other. In the third case of Lindsay *et al.* the interstitial tissue of the glomeruli showed a deposition of granular non-staining material and the collecting tubules showed epithelial swelling with similar material in the cells; the majority of the glomeruli had normal epithelium though several showed epithelial crescents; most of the convoluted tubules were normal. In the seventh case of the same authors there was moderate vacuolation of the cytoplasm of the cells of both limbs of Henle's loop, but the most striking vacuolation of the tubular cytoplasm was seen in the larger collecting tubules near the renal pelvis. The connective tissue adjacent to the renal pelvis showed swelling and vacuolation of the cells and similar changes were seen in the pelvic connective tissue. This case also showed increased epithelial cellularity of the glomeruli and diminished vascularity of the glomerular capillaries, also thickening and fraying of the basement membranes of the tufts: two other cases showed similar features.

Three cases showed evidence of early glomerulonephritis with epithelial crescent formation. One of these was the third case of Lindsay *et al.* mentioned in connexion with the deposition of granular material in the interstitial tissues of the glomeruli.

Three cases had fatty degeneration of convoluted tubules and another cloudy swelling. In one case there were scattered vacuolated cells in the interstitial connective tissue.

The Gonads

Morbid Anatomy. These were described as normal in the six cases mentioned. Three were male and three female. Hydrocoele was present in no fewer than four of the male patients; it was bilateral in two.

Histology. Testes were examined in seven cases, but only one ovary was examined. In the testes enlargement and vesiculation were features in both parenchymal and interstitial cells in four cases; two showed these changes in interstitial cells only and one was said to have been normal. In one case characteristic connective tissue cells were described. In another the epididymis and vas deferens were normal. The ovary showed primordial and growing follicles. An occasional small group of foam cells was present in the stroma.

Urinary Tract and Prostate

Morbid Anatomy. No abnormalities were mentioned in the six cases reported.

Histology. The prostate was examined microscopically in two cases. It was normal in one but the acinar cells showed characteristic vacuolation in the other.

The Lymph Nodes

Morbid Anatomy. Enlargement of lymph nodes was mentioned in six cases. In five they were abdominal and in one tracheo-bronchial. In one case they were as much as 1½ cm. in diameter. They were soft and pale yellowish-pink. In another case they were strikingly yellow.

Histology. Nodes from nine cases were examined. In most cases the peripheral lymphoid follicles were small and indistinct, and the sinusoids were widened, the lining reticulo-endothelial cells being enlarged and vesicular and the lumina containing many similar cells.

Thymus Gland

Morbid Anatomy. This gland was described as enlarged in four of the 14 cases in which it was mentioned and normal in 10.

Histology. Microscopic examination was done in 14 cases. In several cases the lobules were described as large. Most showed a diminution in the number of lymphocytes and diffuse enlargement and vesiculation of reticular cells, particularly in the medullary zones.

The Pituitary Gland

Morbid Anatomy. This gland, described in 13 cases, was said to have been normal in seven cases and enlarged in six. The sella turcica was described in 14 cases and it was enlarged in all except one.

Histology. This was reported in 14 cases. The anterior lobe was examined in 10 cases and was normal in only two. In eight cases there was pronounced vacuolation of most of the cells, particularly the chromophobe cells. The nuclei of some of the heavily infiltrated chromophobes tended to be pyknotic. De Lange *et al.* (1944) observed some colloid-like masses and some diffuse increase of connective tissue. In our case most of the normal cells, which were scanty, were oxyphilic. Infiltration of the anterior pituitary cells appears to be a feature in a high proportion of cases, if not all.

The posterior lobe was described in eight cases. It was said to be normal in five cases and abnormal in three. The latter three were reported by Lindsay *et al.* (1948) and in them the glial cells showed abundant vacuolated cytoplasm with fragmentation of the glial fibres.

The middle lobe was mentioned in two cases and appeared to be normal in one and cystic in the other.

Pineal Gland

Morbid Anatomy. This gland was mentioned in three cases. It was said to have been normal in one, small in one, and absent in one.

Histology. Microscopy was done in two cases. It was normal in one but in the other many of the glial and pineal cells were enlarged and had increased amounts of clear, vesicular cytoplasm.

The Thyroid Gland

Morbid Anatomy. This gland was described as normal in eight cases and enlarged in one case.

Histology. Microscopy was done in 11 cases. The gland looked normal in six cases. In two the acini were enlarged and in two there were many small follicles resembling the foetal type of gland. In another there was a considerable degree of parenchymatous atrophy with pronounced fibrosis. In the two cases with acinar enlargement most of the epithelial cells had abundant, clear vacuolated cytoplasm. It would thus appear that the thyroid gland usually does not show characteristic changes in gargoylism.

The Adrenal Glands

Morbid Anatomy. This was mentioned in nine cases. Eight appeared normal and the glands were small in one.

Histology. Microscopy was done in 13 cases. The appearance was normal in eight. The medullary cells showed characteristic swelling and vacuolation in four cases, while occasional foam cells were observed in the connective tissue in another case.

The Pancreas

Morbid Anatomy. No abnormality was noted in 10 cases mentioned.

Histology. Ten cases were examined. No characteristic infiltration of the cells was observed in any of them. Vacuolation of some connective tissue cells was mentioned in one case.

Parathyroid Glands

Histology. Microscopy was done in only one case and the appearance was normal.

The Lung and Pleura

Morbid Anatomy. Nothing significant was observed in any of the cases.

Histology. Microscopy was done in 14 cases. In nine there was evidence of cellular infiltration. In most of these the alveolar walls were greatly thickened and in some they showed fibrosis and infiltration with lymphocytes and plasma cells. Distension and vesiculation of the alveolar epithelium was a constant feature, also the presence of many of these altered cells in the alveolar spaces. Numerous vacuolated macrophages were also found in the alveoli. Characteristic cartilage changes were described in the bronchial cartilage in four cases. Other changes mentioned were characteristic infiltration in the tracheal epithelium and fibrous thickening in the trachea and bronchi.

The pleura was described in only a few cases. It usually showed fibrous thickening and some infiltration with lymphocytes and with macrophages showing the characteristic distension and vesiculation.

The Alimentary Tract

Morbid Anatomy. This was mentioned in 10 cases and all appeared normal.

Histology. Observations were recorded in seven cases. In four the ganglion cells in the intestine were swollen and vesiculated; in one of these the ganglion cells in the oesophagus and pylorus were similarly affected. In our case a few foam cells were seen among the lymphoid cells of a Peyer's patch. In one case the squamous epithelium of the oesophagus showed vesiculated cytoplasm; in another the outer squamous cells of the tongue had a large amount of clear vacuolated cytoplasm with indistinct cell outlines and invisible intercellular bridges. No abnormality was observed in one case.

The Gall Bladder and Bile Ducts

Morbid Anatomy. The gall bladder was mentioned in 11 cases and the main bile ducts in four. In one case the gall bladder mucosa showed some yellow stippling.

Histology. Microscopy of the gall bladder was done in two cases. It was normal in one case but in the other the connective tissue showed characteristic changes in the fibrocytes and collagen fibres.

Bone Marrow

Histology. This was described in four cases. It was normal in three cases, but infiltrated macrophages and connective tissue elements were observed in the marrow spaces of teeth, the mandible, and the petrous temporal bone in the very detailed seventh case of Lindsay *et al.* They did not observe these changes in the ribs or spine.

The Skin

Morbid Anatomy. This has not been described.

Histology. This was described in five cases. No abnormality was observed in two cases, but two showed enlargement and vacuolation of the epithelial cells of sweat glands and hair follicles. In one of these cases many of the squamous cells were vacuolated also.

Skeletal Muscle

Histology. Microscopy was done in only one case. Muscle fibres taken from several areas were normal, but the perivascular connective tissue showed characteristic changes.

The Leucocytes

Reilly (1935, 1941) described abnormal eosinophilic granules in the leucocytes in gargoylism. They varied in size from fine, dust-like to large, coarse particles. Usually 60% to 90% of the neutrophils contained them, though the percentage of cells containing them varied widely. Lindsay *et al.* examined blood films in seven of their series and found these abnormal granules in the cytoplasm of the neutrophils in four cases. The granules were present in smaller numbers in the monocytes but were not seen in the lymphocytes. They were observed in marrow cells in only one case. Appropriate staining methods suggested that the granules consisted of glycogen.

THE CELLULAR LESION

The review of the pathology of the disease has shown how almost all the tissues of the body may be affected. Certain tissues, such as the brain, liver and spleen, are invariably involved in typical cases, whereas other tissues such as the lungs, pancreas and suprarenal glands frequently show no abnormality. The changes are essentially similar in all affected tissues, and have features which suggest a disease of abnormal storage.

The characteristic cellular lesion is cytoplasmic swelling which usually causes enlargement of the cell. The cytoplasm may be clear, vacuolated or granular. Most types of cell are involved in the abnormal process: epithelial cells such as those of the liver, anterior lobe of the pituitary gland, epidermis and skin glands; reticulo-endothelial cells in many tissues, particularly in the lymph nodes and spleen, and nerve cells in all parts of the central nervous system. The pathological changes were as pronounced in the mesodermal connective tissues as anywhere. Chondrocytes, osteocytes and fibrocytes all showed characteristic enlargement and vacuolation. Lindsay *et al.* demonstrated the universality and characteristic appearance of the connective tissue changes very clearly in their Case VII which had a much more detailed histological examination done than any other reported case of the disease. They believe that the widespread connective tissue involvement is responsible for the malformation of the skeleton and soft tissues and for the diminished growth. Abnormal osteoblastic activity, particularly in the epiphyses, was undoubtedly the main cause of retarded and aberrant skeletal growth. The same authors also believe that the abnormal microscopic appearance of the intercellular matrix in many situations is a logical accompaniment of the cytological changes, since the matrix supporting these cells is derived from their cytoplasm. The intercellular substance had usually lost its normal fibrillary appearance and the collagenous fibres appeared swollen and

imparted an abnormally homogeneous appearance to it.

THE ABNORMAL DEPOSIT

The nature of the abnormal deposit in gargoylism has been the subject of much speculation, also of detailed investigation in several of the reported cases. Ellis, Sheldon and Capon (1936), in reviewing the features of the 17 cases reported up to that time, had little pathological evidence on which to speculate, only the incomplete report by Tuthill on Hurler's (1919) case, but, on the basis of the analogy with established diseases of lipoid storage, they suggested that gargoylism might prove to belong to that group. Since that time gargoylism has generally been classed as a lipoidosis though proof has never been forthcoming. Washington (1948) coined the term ' lipochondrodystrophy ' which is often used in connexion with the disease. Within the last few years several authors have expressed doubt about the disease being a lipoidosis because of the persistent failure to demonstrate the lipoid nature of the deposits by staining methods, or by chemical analysis of heavily infiltrated tissues. It has been suggested by De Lange *et al.* (1944) and Strauss (1948) that the deposit might be a glycogen compound, and Lindsay *et al.* (1948) claim to have demonstrated by a histochemical method that the substance is glycogen or a glycogen compound.

An attempt was made to identify the abnormal deposit in three cases before the publication of the series of Lindsay *et al.* Histochemical examination of the deposit was carried out in three cases: the brain was examined in the case of Tuthill and in the first case of Ashby *et al.*, and various tissues in the case of Kressler and Aegerter. Chemical analysis of brain tissue was performed in one, the first case of Ashby *et al.* Investigation of the deposit with a variety of methods of fixation and of staining methods did not yield consistent results or enable identification of the substance to be made in any of the three cases studied. The deposit was, for instance, stained by Scharlach red in the case of Tuthill and the first case of Ashby *et al.*, but not in the case of Kressler and Aegerter. Moreover, in the case of Ashby *et al.*, in which the deposit was studied more thoroughly than in the other cases, the intracellular and extracellular staining reactions were dissimilar, that for Scharlach red, for instance, being intracellular positive and extracellular negative.

Biochemical analysis of the brain tissues in the first case of Ashby *et al.* also failed to identify the abnormal deposit. They compared the results in their case with the results of analysis in three controls. The total lipoids of the white and grey matter were slightly subnormal, but the cerebroside content was very low in the cortex, being only about half that of the controls. There was no significant reduction of cerebrosides in the white matter. By a process of exclusion with the aid of solubility and melting-point tests and staining reactions, they came to the conclusion that the extracellular lipoid in the perivascular region of the brain in their case was composed mostly of cerebrosides, namely phrenosin or kerasin or a mixture of both. The concentration of cerebrosides in the perivascular spaces appeared to these workers to be in process of removal from the grey matter, which, as stated, showed a reduction of cerebroside to half the normal amount. Such a process is a result of cerebral degenerative disease and has no direct bearing on the nature of the intracellular deposit in the nerve cells and the parenchymal cells of other organs.

Lindsay *et al.*, in several of their cases, demonstrated small amounts of lipoid in many of the swollen cells with various histological stains, but the lipoid which these stains revealed did not account for the tremendous increase in the volume of cytoplasm and often was not greater than the amount normally found. They felt, therefore, that the possibility of the stored substance being a lipoid seemed remote. The intracellular substance could not be stained consistently with a variety of the common protein stains, and was presumed, therefore, not to be purely protein in nature. They failed to demonstrate glycogen in significantly large amounts in tissue fixed in alcohol from two of their cases. The interval between death and necropsy in their cases was long and they felt that post-mortem glycolysis of fairly large quantities of glycogen had probably occurred before fixation of the tissues. This hypothesis led these workers to investigate fresh biopsy specimens for glycogen and they claimed to have demonstrated abundant intracellular glycogen deposits in the swollen liver, costal cartilage and fibial epiphyseal cells which they examined; it was present in quantities sufficient to account for the cellular enlargement. The specimens were fixed in a solution of diosane, trinitrophenol, formaldehyde and acetic acid and stained by the Feulgen-Bauer method. With similarly fixed hepatic tissue from a case of von Gierke's disease as a control, incubation of hepatic tissue with saliva caused a loss of the granular material which had stained with the Feulgen-Bauer method. They regarded this evidence as proof that the carbohydrate stored in the hepcellsatic in gargoylism is a polysaccharide, presumably glycogen, rather than a less complex carbohydrate.

These workers consider that the glycogen may be combined in some instances with a protein as a glycoprotein or mucoprotein. They believe that similar histochemical examination of the other tissues affected in gargoylism will reveal intracellular storage of glycogen or a glycoprotein wherever they are found.

De Lange *et al.* (1944) described an abnormal galactose tolerance test in their case, the blood level being unduly elevated and sustained. Lindsay *et al.* did carbohydrate tolerance tests in six of their patients; galactose tolerance tests were done in three and an abnormal result was obtained in one. In this case the blood galactose level remained elevated for an unduly prolonged period, a result which could be explained by structural alteration of the hepatic cells. Blood glucose curves after administration of insulin and adrenalin were normal in this case. These authorities believe that the large deposits of carbohydrate in gargoylism may be metabolically inactive and may not be involved in the turnover of an otherwise normal carbohydrate metabolism. They think that its possible combination with protein as a glycoprotein supports this thesis.

The quantitative differential lipoid analyses of the liver and spleen done by us in Case 1 (Tables 1 and 2) showed values within the normal range. This demonstrates the absence of an increase of any lipoid fraction in a typical case of gargoylism. The disease can therefore no longer be considered as a lipoid storage disease resulting from an abnormal intracellular lipoid metabolism. There is no doubt that staining reactions may give a very misleading impression of the amount of a tissue metabolite present in organs; only quantitative chemical methods give a reliable indication of an increase or decrease. Unfortunately, Lindsay *et al.*, who claimed to have demonstrated the deposit in gargoylism to be a complex polysaccharide, based their conclusions on qualitative staining methods only. Without the support of quantitative chemical analyses of the stained substances in the affected organs, and in the corresponding organs of controls, their interesting hypothesis remains unproven. There was no evidence of abnormal lipoid or glycogen content in the fresh biopsy specimen of liver in our Case 3 in which there was typical vacuolation of the liver cells (Figs. 27 and 28); the specimen was examined both by standard staining methods for lipoid and glycogen and by quantitative chemical analysis.

There is no satisfactory evidence that the deposit in gargoylism is either a lipoid or pure glycogen. It should be possible to demonstrate by biochemical methods whether it is, or is not, a glycogen compound. No opportunity of doing quantitative estimations of glycogen compounds, necessarily by indirect means, on fresh tissues obtained from typical cases of gargoylism should be missed. In this way it should be possible to prove or disprove the latest theory of the pathogenesis of this peculiar, inherited, metabolic disease.

SUMMARY

Three cases of gargoylism are recorded.

An extensive study of the pathology and biochemistry in one case was made. Biopsy specimens in the other two cases were examined histologically, and in one of these also biochemically.

The gross vascular and meningeal pathology were notable features in the child who came to necropsy. These features had not been described before, but have since been observed by others.

The literature relating to the pathology and biochemistry is reviewed in detail.

The pathogenesis of the disease remains unproven. The intracellular deposit is neither a lipoid nor glycogen. Further biochemical studies should demonstrate whether the substance is a glycoprotein or mucoprotein as has been suggested.

We are grateful to Dr. D. N. Nicholson for permission to publish Case 3, and to Dr. W. Blackwood for his neuropathological examination and report in Case 1.

REFERENCES

Ashby, W. R., Stewart, R. M. and Watkin, J. H. (1937). *Brain*, **60**, 149.
Berliner, M. L. (1939). *Arch. Ophthal., Chicago*, **22**, 97.
Cordes, F. C. and Hogan, M. J. (1942). *Ibid., Chicago*. **27**, 637.
Lange, C. De (1942). *Psychiat. neurol. Bl., Amst.*, **46**, 2.
——, Gerlings, P. G., De Kleyn, A. and Lettinga, T. W. (1944). *Acta paediatr., Uppsala*, **31**, 398.
Debré, R., Marie, J. and Thieffry, S. (1946). *Sem. Hóp., Paris*. **22**, 309.
Ellis, R. W. B. (1937). 'British Encyclopaedia of Medical Practice.' vol. 5, p. 496.
——, Sheldon, W. and Capon, N. B. (1936). *Quart. J. Med.*, **29**, (n.s. 5) 119.
Green, M. A. (1948). *J. Neuropath.*, **7**, 399.
Höra, J. (1939). *Virchows Arch.*, **305**, 298.
Jervis, G. A. (1950). *Arch. Neurol. Psychiat., Chicago*, **63**, 681.
Kny, W. (1942). *Z. Kinderheilk.*, **63**, 366.
Kressler, R. J. and Aegerter, E. E. (1938). *J. Pediat.*, **12**, 579.
Lindsay, S. (1950). *Brit. Heart J.*, **12**, 17.
——, Reilly, W. A., Gotham, T. J. and Skahen, R. (1948). *Amer. J. Dis. Child.*, **76**, 239.
MacIntyre, D. S., Pedersen, S. and Maddock, W. G. (1941). *Proc. Soc. exp. Biol., N.Y.*, **47**, 354.
Magee, K. R. (1950). *Arch. Neurol. Psychiat., Chicago*, **63**, 282.
Njå, A. (1945). *Acta paediatr., Uppsala*, **33**, 267.
Reilly, W. A. (1935). *Endocrinology*, **19**, 639.
——, (1941). *Amer. J. Dis. Child.*, **62**, 489.
Rochat, G. F. (1942). *Ophthalmologica*, **103**, 253.
Schmidt, M. B. (1942). *Zbl. allg. Path. path. Anat.*, **79**, 113.
Stoeckel, K. H. (1941). *Mschr. Kinderheilk.*, **86**, 348.
Straus, R., Merliss, R. and Reiser, R. (1947). *Amer. J. clin. Path.*, **17**, 671.
Strauss, L. (1948). *Amer. J. Path.*, **24**, 855.
Tuthill, C. R. (1934). *Arch. Neurol. Psychiat., Chicago*, **32**, 198.
Washington, J. A. (1948). Brennemann's 'Practice of Pediatrics', ed. McQuarrie, I. J., vol. 4, Ch. 30. Hagerstown, Maryland.
Wolff, D. (1942). *Laryngoscope, St. Louis*, **52**, 218.
Zeeman, W. P. C. (1942). *Acta Ophthal., Kbh.*, **20**, 40.

BRONCHOSCOPIC TREATMENT OF ATELECTASIS IN CHILDREN

BY

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Pulmonary atelectasis in children was often found to have cleared soon after diagnostic bronchoscopy. Re-ventilation occurred even in children in whom the collapse had resisted the usual methods of treatment during preceding weeks or months. It was, therefore, decided to bronchoscope every child with pulmonary collapse provided the collapse was known to have existed for more than five weeks. In a few children the examination was carried out sooner than five weeks after the existence of the collapse was known, either because the indications were urgent or because the collapse could reasonably be assumed to have existed for a considerable time.

Bronchoscopy was carried out on 50 consecutive children admitted with atelectasis, unselected apart from the exclusion of cases due to foreign body, and irrespective of the presumed aetiology of the collapse. Sixty-seven collapsed lobes were present in these 50 children, whose ages ranged from 17 days to 12 years, the average age being 3 years 11 months. The lobes involved were: right upper, 14; right middle, 17; right lower, 21; left upper (including lingula), 7; left lower, 8. In 15 cases several lobes were collapsed. The collapse was known to have existed from three days to two years four months, the average being 15½ weeks.

Antero-posterior and lateral radiographs were taken 10 days after the examination. The effect of bronchoscopic aspiration was considered good if the lung had re-expanded after 10 days, fair if it had cleared one month after bronchoscopy and poor if the collapse persisted.

Results

Of the total of 67 collapsed lobes, 34 (51%) cleared in 10 days, 13 (19%) in a month, and 20 (30%) failed to clear (Table 1). It became obvious that in children with positive Mantoux reactions the collapse was less likely to clear than in those in whom the reaction was negative. The 21 children with a positive Mantoux reaction had 26 collapsed lobes. Of these, eight (31%) had a 'good' result, five (19%) a 'fair' result and in 13 (50%) the result was 'poor' (Table 2). Of the 29 children whose 41 collapsed lobes were not associated with a primary tuberculous complex, 26 (63%) had a 'good' result, eight (20%) a 'fair' result, and in seven (17%) the result was 'poor' (Table 3).

TABLE 1
EFFECT OF BRONCHOSCOPY ON 67 UNSELECTED ATELECTATIC LOBES

Lobe	Good	Fair	Poor	Total
R.U.	5	2	7	14
R.M.	8	3	6	17
R.L.	13	6	2	21
L.U.	4	0	3	7
L.L.	4	2	2	8
Total	34	13	20	67

TABLE 2
EFFECT OF BRONCHOSCOPY ON 26 ATELECTATIC LOBES IN CHILDREN WITH PRIMARY TUBERCULOUS COMPLEX

Lobe	Good	Fair	Poor	Total
R.U.	2	1	3	6
R.M.	2	1	5	8
R.L.	3	2	1	6
L.U.	1	0	3	4
L.L.	0	1	1	2
Total	8	5	13	26

TABLE 3
EFFECT OF BRONCHOSCOPY ON 41 ATELECTATIC LOBES IN CHILDREN WITH NEGATIVE MANTOUX REACTIONS

Lobe	Good	Fair	Poor	Total
R.U.	3	1	4	8
R.M.	6	2	1	9
R.L.	10	4	1	15
L.U.	3	0	0	3
L.L.	4	1	1	6
Total	26	8	7	41

Bronchoscopic Findings

The difference in the response of Mantoux positive and Mantoux negative children is not surprising. It is well known that the atelectasis commonly found in primary tuberculous infection

('epituberculosis') is due to enlarged glands pressing on a bronchus from without (Jones, Rafferty and Willis, 1942), leading first to narrowing and later to occlusion of the bronchial lumen, with absorption collapse behind the block.

In these circumstances the introduction of a sucker into the bronchus behind the obstruction cannot be expected to lead to re-aeration of the collapsed segment as the obstruction is not removed. In several instances, however, bronchoscopy had a good effect. In three cases rupture of a tuberculous gland had led to extreme, sudden dyspnoea, associated with cyanosis, pallor and shock. Removal of glandular debris and caseous material resulted in re-ventilation of the collapsed lobe or lobes, and may have been of life-saving importance (Görgényi-Göttche and Kassay, 1947). In several other cases the lobe re-expanded after the removal of secretions from behind a stenosed part of the bronchus.

The bronchoscopic appearances in these children with tuberculous collapse were similar to those described by Hutchison (1949). In 13 an enlarged gland was seen to be pressing on one or more bronchial openings. In nine instances a velvety, injected mucosa, as described by Jackson and Jackson (1950), was found overlying the enlarged gland, and once a shallow ulcer was found. No local treatment by silver nitrate or dilation was considered necessary as the children with parenchymal infiltration or tuberculous bronchopneumonia were treated systemically with streptomycin or P.A.S. In six cases a bronchial swab revealed tubercle bacilli on direct smear or culture, though examination of stomach washings, material coughed upon a laryngeal mirror and stool examinations had repeatedly given negative results.

Of the 41 collapsed lobes not associated with a primary tuberculous complex, 16 were due to whooping cough, 11 to pneumonia, five to measles, three to massive collapse associated with empyema, three to atelectasis in bronchiectatic lobes, two were congenital and one was due to a persistent antral infection. Similar aetiological factors have been described by Oswald (1947). All cases of post-pertussis collapse had persisted for more than five weeks before they were bronchoscoped, and all had been treated with sulphonamides, antibiotics or postural drainage on one or more occasions without success. It was thought essential to delay bronchoscopy in these post-pertussis cases in view of Lees' (1950) finding that the majority of collapsed lobes had cleared by the fifth week.

In these non-tuberculous patients bronchoscopic aspiration led to re-ventilation of the collapsed lobes in 83% of cases within one month. In several instances no obstruction was seen, and even so the collapse cleared after bronchoscopy. It is possible that the hyperventilation and coughing occasionally associated with the anaesthetic may have led to clearance in these cases. On the other hand this unexplained clearance happened no more frequently in children in whom induction and recovery were stormy than in those anaesthetized by experts with pentothal and curare.

In 11 cases organisms were grown from a bronchial swab. The organisms found were *Staph. aureus*, *N. catarrhalis*, *H. influenzae*, pneumococci, *Strep. pyogenes* and diphtheroids. One neoplasm, not responsible for the atelectasis, was found, and the biopsy section report was of 'a small nodule of fibrous tissue consisting of spindle-shaped cells enmeshed in a loose collagenous matrix. The appearance suggests that it is a small benign fibroma; it might be of neurofibromatous origin' (Dr. M. O. Skelton, Lewisham Group Laboratory).

Technique

The examinations were carried out with a Negus type of bronchoscope, introduced without a laryngoscope. Notwithstanding Chevalier Jackson's advice, all children were given a general anaesthetic as it was felt that psychic trauma might otherwise result. Also, the examination can be carried out much more quickly in an unconscious than in a struggling child. The anaesthetic used was usually pentothal and curare, but several examinations were carried out under trilene, nitrous oxide or ether anaesthesia. In no case did anaesthetic complications arise. It was found that the appearance of the trachea and carina was often markedly affected by the use of curare. The posterior tracheal wall was slack and bulged into the tracheal lumen, and similarly the carina was 'slacked off' so that its edge became blunt and shortened antero-posteriorly. In several cases the introduction of lipiodol was attempted, using a specially adapted sucker which was passed through the bronchoscope. Whilst individual lobes could be well filled, attempted filling of the whole side gave poor results because the child could not be positioned satisfactorily with the bronchoscope *in situ*.

There were no post-operative complications, and oil aspiration pneumonia due to lubrication of the bronchoscope with liquid paraffin (Brimblecombe, Crome and Tizard, 1951) did not occur. As the examination hardly ever lasted longer than 10 minutes local and general upset was negligible. There was no difference in the course of those children who had a penicillin cover for 24 hours before and 48 hours after bronchoscopy, and those who did not.

Discussion

It has long been recognized that atelectasis either alone (Lander and Davidson, 1938) or in the presence of infection (Tannenberg and Pinner, 1942) is the precursor and main cause of bronchiectasis (Coryllos and Birnbaum, 1929; Anspach, 1934). The parts of the lung most commonly involved in atelectasis are the same as those most commonly affected by bronchiectasis (Lees, 1950). There is general agreement that the likelihood of bronchiectasis developing in an atelectatic lobe depends on the length of time the lobe remains collapsed (Nicholson, 1949). Clearly, therefore, the recognition and early and effective treatment of atelectasis in childhood are of the utmost importance if permanent bronchial dilatation is to be avoided.

Various methods of treatment have been used, such as inhalation of carbon dioxide, postural coughing and postural drainage, heavy percussion of the chest wall and breathing exercises. Many of these methods are difficult or impossible to carry out in children, and in any case they are unlikely to be successful if the collapse has persisted for any length of time (Ellis, 1933). On the other hand bronchoscopic aspiration of an obstructed bronchus is frequently effective in clearing a collapsed lobe, and has the additional advantage of allowing the cause of the collapse to be established in a large number of cases (Holinger, 1950).

Summary

Bronchoscopic aspiration in cases of atelectasis in children frequently leads to re-expansion of the collapsed lobe, and therefore prevents bronchiectasis. Results are better when the collapse is due to an acute infection, and less good if collapse results from pressure by glands on a bronchus. The general and local upset following bronchoscopy in children is slight.

I wish to express my thanks to Dr. H. S. Banks for his valuable advice and for referring some of the cases of post-pertussis collapse, also to Dr. J. M. Piney and Dr. W. S. Hart who gave many of the anaesthetics.

References

Anspach, W. E. (1934). *Amer. J. Dis. Child.*, **47**, 1011.
Brimblecombe, F. S. W., Crome, L. and Tizard, J. P. M. (1951). *Archives of Disease in Childhood*, **26**, 141.
Coryllos, P. N. and Birnbaum, G. L. (1929). *Amer. J. Roentgenol.*, **22**, 401.
Ellis, R. W. B. (1933). *Archives of Disease in Childhood*, **8**, 25.
Görgényi-Göttche, O. and Kassay, D. (1947). *Amer. J. Dis. Child.*, **74**, 166.
Holinger, P. H. (1950). Reported in *Amer. J. Dis. Child.*, **79**, 1143.
Hutchison, J. H. (1949). *Quart. J. Med.*, N.S. **18**, 21.
Jackson, C. and Jackson, C. L. (1950). In 'Bronchoesophagology', Philadelphia.
Jones, E. M., Rafferty, T. N. and Willis, H. S. (1942). *Amer. Rev. Tuberc.*, **46**, 392.
Lander, F. P. L. and Davidson, M. (1938). *Brit. J. Radiol.*, **11**, 65.
Lees, A. W. (1950). *Brit. med. J.*, **2**, 1138.
Nicholson, D. P. (1949). *Archives of Disease in Childhood*, **24**, 29.
Oswald, N. C. (1947). *Proc. roy. Soc. Med.*, **40**, 736.
Tannenberg, J. and Pinner, M. (1942). *J. thorac. Surg.*, **11**, 571.

VARIATION IN THE PROTEOLYTIC ACTIVITY OF CHILDREN'S STOOLS

A STUDY OF MECONIUM AND STOOLS FROM NORMAL AND ILL CHILDREN

BY

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In most paediatric clinics the examination of stools for tryptic activity has become a routine screening test as an aid to the diagnosis of fibrocystic disease of the pancreas.

The test is an old one (Hecht, 1908), and although recently re-introduced by Shwachman, Patterson and Laguna (1949) for use in fibrocystic disease, the examination of stools for trypsin has in the past been proposed as an aid to the diagnosis of other diseases such as rickets (Lukacs, 1926).

There is a physiological and a little experimental basis for examining faeces for trypsin as an indication of pancreatic function. It is known that the pancreas is the gland chiefly responsible for the intestinal secretion of trypsin and alkali, and it has been shown in animals that if all the pancreatic ducts are tied tryptic activity disappears from the stools (Carpi, 1923).

The clinical advantage of testing for tryptic activity of stools lies in its simplicity compared with the obviously more valuable examination of aspirated duodenal juice. On occasion there is considerable difficulty in obtaining duodenal samples and the procedure is not suitable as a rapid out-patient routine.

The amount of pancreatic secretion varies greatly, both with the individual and the diet (Thomas, 1950; Kahn and Klein, 1932; Snyder and Liume, 1936; Abramson, 1935), and it is probable that any residue in the faeces would vary to an even greater extent. To assess the clinical value of estimating faecal trypsin it is necessary to know the extent of this variation.

Klumpp and Neal (1930) found a relatively high level of trypsin secretion in infancy compared with that in later childhood, and Maday and Dancis (1947) found no depression of proteolytic enzymes in immature infants. McDougal (1950) found normal enzyme activity in the presence of severe malnutrition; four of 165 children showed a transitory partial suppression of activity in infections. Maddock, Farber and Shwachman (1943) found a smaller rise in trypsin levels after stimulation with secretin in six patients with malnutrition compared with five normal infants.

Veghelyi (1949), studying children over the age of 11 months, found no difference in duodenal enzyme value at different ages, and he was unable to relate the fluctuation in levels that he obtained with diet. His aim, however, was to establish mean levels and he used pooled specimens which would eliminate recording the widest variation in enzyme content.

In the recent clinical use of testing for faecal trypsin it was soon realized that anomalous results occurred; that children with gross fibrocystic disease can on occasion show tryptic activity in the stool (Johnstone, 1950; Johnstone and Neter, 1951), and from our own observations, that no tryptic activity may be found in apparently normal children.

It is also obvious that fibrocystic disease is neither clinically (Gibbs, Bostick and Smith, 1950) nor histologically (Andersen, 1948; Emery, 1951a) an 'all or none' disease, and a gross clinical syndrome may only be expected in what are probably the severe and irreversible cases.

It seemed necessary, therefore, to ascertain the degree of variation in faecal tryptic activity of normal children and also the variation in tryptic activity related to other incidents in the child.

Material and Methods

Two separate series of stools were obtained.

For the assessment of the normal tryptic range three groups of 100 normal children were used. Meconium was obtained from 100 normal infants born at a municipal maternity unit. In all cases the first specimen of meconium obtained from the child was examined. The stools from older children were from my own and my colleagues' children, 'well baby' welfare clinics, children in residential hostels for normal children in the Sheffield region, and a few selected normal children admitted to the surgical side of the Children's Hospital for surgical anatomical conditions such as strabismus.

In the general series, which contained over 1,000 stools, the stools were obtained from children in the

Sheffield Children's Hospital and in long stay and convalescent hospitals in the Sheffield area. No selection was made other than excluding cases of fibrocystic disease and very ill children.

Stools were collected in waxed cartons and examined usually within 24 hours of being passed, resting meanwhile in the refrigerator.

Tryptic activity was estimated using a simplified modification (Emery, 1951b) of that described by Andersen and Early (1946). The gelatine photographic film method was not used as it was no more rapid and thought to introduce too many uncontrollable factors. The recent observations of Gaffney (1951) appear to confirm this view.

Specimens in the normal series were examined to a final negative dilution whereas those in the general hospital series were examined at a dilution of 1 in 5, 10, 50 and 100 only.

Results

Tryptic Activity in Stools from Normal Healthy Children. These values are shown in Fig. 1.

MECONIUM. In the consecutive series from 100 normal newborn infants one specimen had no tryptic activity, two had tryptic activity only at a dilution of 1 in 2, four at a dilution of 1 in 4 and 12 at a dilution of 1 in 8. The distribution curve (Fig. 1) has a mean titre of around 1 in 30.

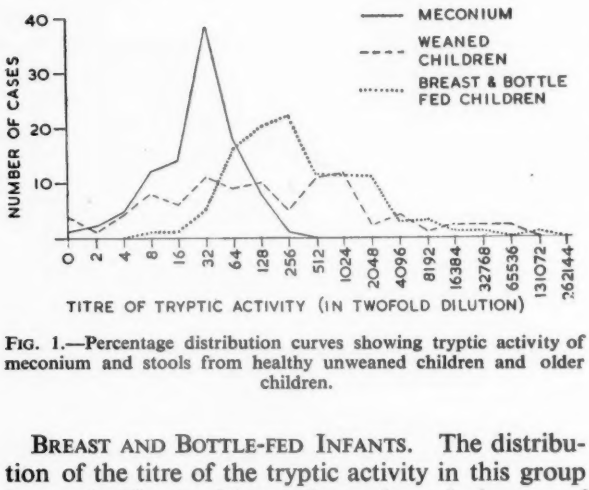

FIG. 1.—Percentage distribution curves showing tryptic activity of meconium and stools from healthy unweaned children and older children.

BREAST AND BOTTLE-FED INFANTS. The distribution of the titre of the tryptic activity in this group is seen in Fig. 1. No specimen showed absence of activity, or activity only to a dilution of 1 in 2 or 1 in 4. One showed activity at a dilution of 1 in 8 and two at 1 in 16. The mean level of tryptic activity is in the region of 1 in 150. The tryptic activity in this group is higher than that in the first specimen of meconium.

WEANED CHILDREN ON MIXED DIETS UP TO THE AGE OF 7 YEARS. The distribution of tryptic activity in this group (Fig. 1) has approximately the same mean as in the breast-bottle fed infants but the standard deviation of the curve is more than twice that of the younger group of children. Four children showed no tryptic activity, one activity at a dilution of 1 in 2, four at 1 in 4, eight at 1 in 8 and six at 1 in 16.

Variation in Tryptic Activity of Stools in Hospital Patients Related to Other Observations. These variations are considered in relation to the consistency and *p*H of the stool, and to the age, height, weight, nutrition, clinical disease of the child, and to other factors.

TRYPTIC ACTIVITY AND CONSISTENCY OF STOOL. Nine hundred and eighty-nine stools were examined; 763 were described as bulky and soft, and 226 as small and hard. When these stools were analysed in degrees of tryptic activity it was found (Table 1) that the general distribution of numbers with different tryptic activity in the two groups appeared similar; 23% of the small, hard stools compared with 18% of the bulky, soft stools had tryptic activity of 1 in 10 or less.

TABLE 1
TRYPTIC ACTIVITY AND CONSISTENCY OF STOOL

Tryptic Activity	Soft and Bulky	Small and Hard
0	24	12
1/5	28	15
1/10	82	28
1/50	59	21
1/100	570	150
Total	763	226

There is no obvious relationship between the size and consistency of the stools and the tryptic activity.

TRYPTIC ACTIVITY AND *p*H OF STOOL. Of 1,003 stools in which *p*H and tryptic activity (Table 2) were examined, 122 (12%) had a *p*H below 6, 649 (65%) a *p*H between 6 and 8 inclusive and 230 (23%) above 8.

TABLE 2
TRYPTIC ACTIVITY AND PH OF STOOL

Tryptic Activity	pH		
	−6	6–8 (inclusive)	8+
0	7	25	5
1/5	3	27	14
1/10	6	75	30
1/50	7	51	24
1/100	99	471	159
	122	649	232

When the percentage of these showing no tryptic activity or tryptic activity at a dilution of 1 in 5

only are compared, all three groups give almost identical figures.

There appears to be no relationship between the tryptic activity of the stool and its *p*H.

TRYPTIC ACTIVITY RELATED TO AGE. In the general survey of stools the numbers in each age group were as follows (Table 3). Birth to 5 months,

TABLE 3

TRYPTIC ACTIVITY RELATED TO AGE

Tryptic Activity	0-5 months	6 months-11 months	1 year-2 years 11 months	3 years-4 years 11 months	5-13 years
0	3	1	9	2	22
1/5	1	2	4	8	29
1/10	2	2	24	14	69
1/50	3	8	11	14	46
1/100	45	84	160	125	315
Total	54	97	208	163	481

54; 6 to 11 months, 97; 12 months to 2 years 11 months, 208; 3 years to 4 years 11 months, 163; over 5 years, 481.

Stools with no tryptic activity and activity only in a dilution of 1 in 5 showed an incidence of 7·4% in the children under 6 months; 3·1%, 6 to 11 months; 5·3%, 1 to 2 years 11 months; 6·2%, 3 years to 4 years 11 months and 10·6% over 5 years.

With this very artificial grouping the lower incidence of trypsin-free stools over the age of 6 months and the subsequent increase appears to be of more than chance occurrence. None of these were clinically suggestive of the coeliac syndrome.

WEIGHT. Of the 943 instances in which the weight was available, 798 were within normal limits, 142 below normal and 12 above normal. Trypsin was absent in 26 (3·3%) instances of the normal group, twice (1·5%) in the below normal group and once in the over-weight group. If the figures for minimal tryptic activity are included the incidence of minimal tryptic activity is 6·8% in the normal weight and 4·6% in the wasted. There appears to be no correlation between the tryptic activity of the stool and wasting in these children.

HEIGHT. A similar finding to height was found. Of 498 children of normal height, 5% had minimal tryptic activity compared with one (2·5%) of 38 children below normal.

NUTRITION. Seven hundred and ninety-seven specimens were described as being from children of normal nutrition, 165 from wasted and 38 from oedematous.

The proportions showing no tryptic activity

TABLE 4

TRYPTIC ACTIVITY RELATED TO WEIGHT

Tryptic Activity	Normal Range	Below Normal Weight	Above Normal Weight
0	26	2	1
1/5	26	4	—
1/10	91	13	—
1/50	69	10	—
1/100	577	113	11
Total ..	789	142	12

were six (5%) in the wasted, 27 (4·6%) in the normal and one (2·6%) in the oedematous. If those showing activity only in the dilution of 1 in 5 are included the proportions are 12·4%, 10·6% and 10·6%.

The general results of these analyses of weight, height and nutrition are that there appears to be no relation between reduced activity of the stool and general nutrition.

RELATION BETWEEN TRYPTIC ACTIVITY AND CLINICAL DISEASE. The diseases were grouped as (1) gastro-intestinal, consisting of any child admitted for any dietary disturbance or surgical or functional disorder of the alimentary tract (97 case specimens); (2) respiratory (228 case specimens); (3) cardiovascular, the majority children with rheumatic heart disease (185); (4) nephritis (49); (5) other diseases, consisting of a mixed group of largely surgical conditions, many being from an orthopaedic hospital (417); (6) 'coeliac', children showing the coeliac syndrome in whom fibrocystic disease had been eliminated by other means (24).

Of the case specimens with intestinal disease 14%, had no tryptic activity and a further 7% at a dilution of 1/5 only. In the respiratory group seven (3·1%) had none and 13 (5·7%) minimal tryptic activity. In the nephritic group one (2%) had no and four (8%) minimal activity. In the miscellaneous group 11 (2·6%) had none and 34 (8·2%) minimal activity.

It will be noted that there was no difference between the nephritic, respiratory, cardiovascular and miscellaneous groups. The intestinal group showed a surprisingly high incidence, approximately one stool in five showing low activity, an incidence significantly higher than in the miscellaneous group. The ages of the children in the intestinal group showed no gross difference from the other groups.

RELATIONSHIP BETWEEN TRYPTIC ACTIVITY AND MOUTH-ANUS STOOL PASSAGE TIME. Stool passage time, using markers, was investigated in 167 specimens only. No relationship between the time of the intestinal passage and the degree of tryptic activity was found.

TRYPTIC ACTIVITY RELATED TO PRESENCE OF MUSCLE FIBRES IN STOOLS. Muscle fibres were seen microscopically in 658 (66%) of the 1,003 stools examined; in 59 (6%) they were present in very large numbers. No fibres were seen in 345 (34%) of the stools. Relationship between the presence of muscle fibres and tryptic activity is shown in Table 5.

TABLE 5

TRYPTIC ACTIVITY RELATED TO THE PRESENCE OF MUSCLE FIBRES

Tryptic Activity	Presence of Muscle Fibres		
	0	+	++
0	17	16	4
1/5	17	24	3
1/10	37	60	14
1/50	31	48	3
1/100	243	451	35
Total	345	599	59

There appears to be no statistically significant relation between the presence of muscle fibres and tryptic activity.

Discussion

The tube method of proteolytic assay used in this study does not give exactly parallel results with the x-ray gelatine film method. But the results we obtained in children of different age groups are roughly parallel to the figures quoted by Shwachman, Patterson and Laguna (1949) in their 'normal' series, i.e. non-fibrocystic. They found that none of 28 premature infants had negative stool trypsin; 4·3% of 233 infants; 12% of 133 children aged 2-5 years, 46% of 74 children 5 to 10 years and 75% of 32 over 10 years. The corresponding figures in our series are for children under 6 months, 7·4% negative; 6-11 months, 3·1%; 1-2 years 11 months, 5·3%; 3-4 years 11 months, 6·2% and over 5 years, 10·6%, that is to say, there is a similar increase in the incidence of trypsin-negative stools in later childhood.

The distribution curves (Fig. 1) from healthy children illustrate this same tendency, as the spread of distribution appears much greater in the older than in the bottle-breast fed infants.

A possible conclusion from these findings is that the absence of proteolytic activity in the stools in the first years of life is rarer than in later childhood, and thus its occurrence is probably of greater clinical significance.

In older childhood, on the basis of the gelatine film test used by Shwachman *et al.* (1949), a negative reaction may be expected in about a half of the non-fibrocystic stools; in our hands the corresponding figure is around a tenth. The implication of this in the use of this test as a screening test for disease of the pancreas will be obvious. Shwachman *et al.* concluded by stating that 'at least three specimens of stool should be examined and whenever doubt arises duodenal intubation is indicated', but, on the basis of their own findings in the age groups 5 to 10 years, the chance occurrence of three consecutive negative stools would be expected in about 1 in 10 of hospital patients. In our hands the tube dilution method of stool trypsin assay appears to be more sensitive and the chance of a series of three negative stools more than 1/100, i.e. more than ten times less likely than the film method.

It is obvious that the use of stool trypsin in the diagnosis of fibrocystic disease of the pancreas can only be of value if used in conjunction with other features. Consideration should also be given to the observation of Johnstone and Neter (1951), who found positive gelatine film tests in 62% of patients with cystic fibrosis of the pancreas.

It had been partly expected that, in view of the postulated association of pancreatic change with glandular changes in the bronchi, that low trypsin levels would be more than usually common in children with chest infections. This does not appear to be the case.

Among the disease groups studied the incidence of low trypsin activity appeared to be remarkably consistent in all, except those presenting with disorders of the gastro-intestinal tract. This is particularly interesting if related to the observation of Baggenstoss (1948) that in routine necropsies an unusually high incidence of cystic and plugged acini was found in patients dying of infective and obstructive lesions of the alimentary tract. We do not know if the pancreatic changes in his cases or tryptic changes in the present series are primary or secondary to the alimentary disturbance and the present study takes us no further.

Summary

A survey was made of the variation in tryptic activity in meconium and in the stools from normal and general hospital patients.

The tryptic content of meconium appeared to be less than in later childhood.

Weaned children had the same mean level of tryptic activity as unweaned children but showed a greater variation in titre.

Approximately one in 10 of older children had minimal or no tryptic activity in the stools.

No relationship was found between the tryptic activity of the stools and the consistency, *p*H, the presence of undigested muscle fibres in the stools, the height, weight or general nutrition of the children.

An increased incidence of trypsin-low stools was found in cases with disorders of the alimentary tract. No increase was seen in children with respiratory infections, cardiovascular disease or nephritis.

The finding of trypsin-free stools appears to have a higher clinical significance in younger than in older children.

It is a pleasure to acknowledge the help of the nursing staff at the Sheffield Children's Hospital, Nether Edge Hospital, the Jessop Hospital, King Edward Orthopaedic Hospital, Ash House Hospital School, the Moss Residential Nursery, and many other individuals for their assistance in collecting specimens of stool.

REFERENCES

Abramson, L. (1935). *Acta med. scand.*, **86**, 478.
Andersen, D. H. (1938). *Amer. J. Dis. Child.*, **56**, 344.
Andersen, D. H. and Early, M. V. (1942). *Ibid.*, **63**, 891.
Baggenstoss, A. H. (1948). *Arch. Path., Chicago*, **45**, 463.
Carpi, U. (1923). Cited by Vercellotti, G. (1927). *'Osped. maggiore*, **15**, 273.
Emery, J. L. (1951*a*). *Archives of Disease in Childhood*, **26**, 570.
—— (1951*b*). *Ibid.*, **27**, 67.
Gaffney, P. C. (1951). *Pediatrics*, **8**, 82.
Gibbs, G. E., Bostick, W. L. and Smith, P. M. (1950). *J. Pediat.*, **37**, 320.
Hecht, A. F. (1908). *Wien. Klin. Wschr.*, **21**, 1550.
Johnstone, D. E. (1950). *Pediatrics*, **6**, 351.
—— and Neter, E. (1951). *Ibid.*, **7**, 483.
Kahn, J. and Klein, H. M. (1932). *Amer. J. med. Sci.*, **184**, 503.
Klumpp, T. G. and Neale, A. V. (1930). *Amer. J. Dis. Child.*, **40**, 1215.
Lukacs, T. (1926). *Ibid.*, **31**, 235.
McDougall, C. (1950). *Pediatrics*, **5**, 114.
Maddock, C. L., Farber, S. and Shwachman, H. (1943). *Amer. J. Dis. Child.*, **66**, 370.
Madey, S. and Dancis, J. (1949). *Ibid.*, **4**, 177.
Shwachman, H., Patterson, P. R. and Laguna, J. (1949). *Pediatrics*, **4**, 222.
Snyder, W. H. and Lium, R. (1936). *Surg. Gynec. Obstet.*, **62**, 57.
Thomas, J. E. (1950). 'The External Secretion of the Pancreas.' (Amer. Lect. Ser. no. 45.) Springfield, Illinois.
Veghelyi, P. V. (1949). *Pediatrics*, **3**, 749.

THE IMPORTANCE OF STAPHYLOCOCCI IN INFANTILE PARENTERAL GASTRO-ENTERITIS

BY

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(RECEIVED FOR PUBLICATION SEPTEMBER 6, 1951)

The acute nutritional diseases of infants (dyspepsia, gastro-enteritis, enterocolitis, toxicosis) comprise a considerable proportion of infantile diseases, representing nearly 10% of our hospital cases (1940-1950). There was a fall in the number of cases following the peak year 1945 but there has been a steady increase since (Fig. 1).

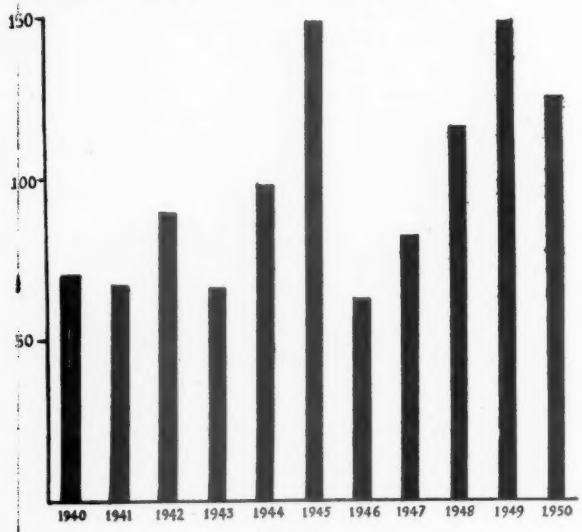

FIG. 1.

Various reasons lead us to believe that the increase during the last few years has been due not to alimentary or primary enteritic forms, but in the main to infectious parenteral forms: (1) the extreme rarity of isolating shigellae or salmonellae from the stools (Tolentino, 1950); (2) the absence of positive agglutinations for shigellae in healthy subjects (Tolentino, 1951, unpublished data), in contrast to the frequency of such agglutinations in healthy subjects in the endemic shigellosis areas (D'Alessandro and Burgio, 1945); (3) variations noted in the seasonal incidence of the disease which showed a peak during the summer of 1945 (Fig. 2) but, in contrast, an irregular curve, less inclined to rise during the summer and remarkably intensified during the winter of 1950 (Fig. 3).

The modern prevalence of enteric forms of parenteral origin also appears in other parts of the world (Hurtado and Aballi, 1949), and appear to be an attribute of the more civilized countries, where hygienic and economic conditions are better (e.g. water supply, use of powdered milk), whereas elsewhere there is a prevalence of primary enteritic disease.

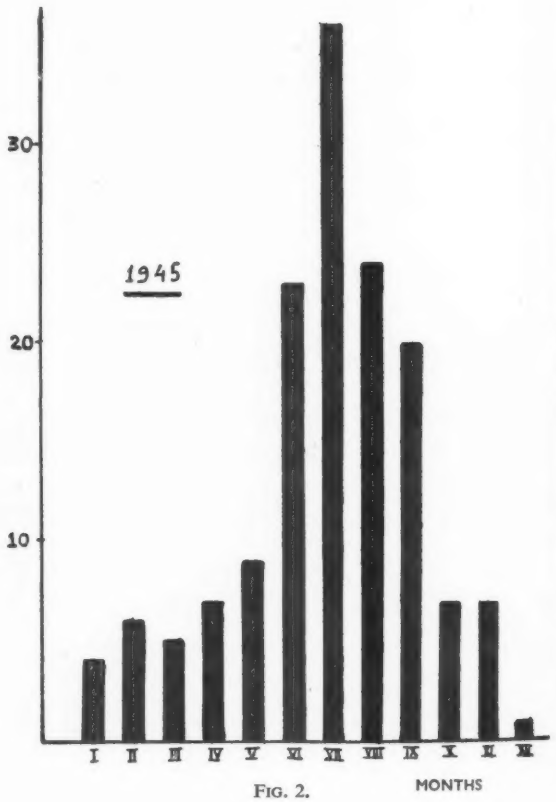

FIG. 2.

In the parenteral forms much attention has been paid to the possibility of a virus aetiology (Light and Hodes, 1949, and others), and indeed, some epidemic forms seem to be almost certainly of this

nature. The fact must not be overlooked, however, that even serious enteritic infections may be caused by pyogenic bacteria, notably staphylococci, and the latter have been the subject of our interest for several years.

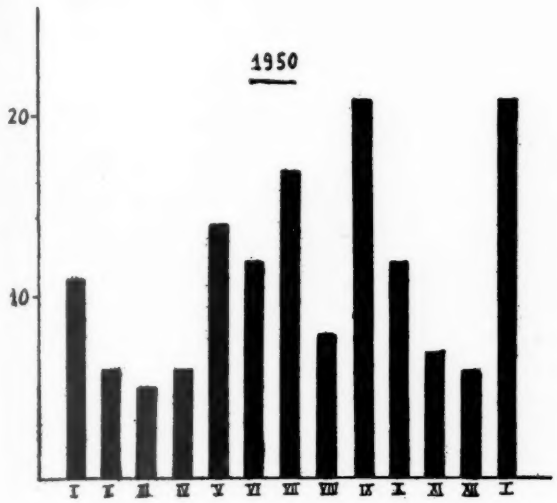

FIG. 3.

The various ways in which gastro-enteritis may develop from an infective parenteral focus may be summarized as (1) decrease of intestinal secretions (in connexion with the disease) and consequent stagnation of the intestinal contents, the ascent of bacteria towards the small intestine, abnormal formations of amines, of organic acids and of bacterial and alimentary toxins, with irritation of the mucous membrane and subsequent hyperperistalsis or antiperistalsis; (2) elimination of toxins from parenteral infective foci through the intestine, and action developed by these toxins on the intestinal mucosa and nerve plexuses; (3) toxic action of bacterial products elaborated in the parenteral foci on the central nervous system, and on the neuro-vegetative centres, with reflex-induced diarrhoea and vomiting.

The first of these mechanisms is authoritatively upheld by American workers (Nelson, 1950). We have been able to demonstrate the truth of the second mechanism by showing the elimination of staphylococcal haemolytic toxins by the intestine and their presence in the stools of children suffering from staphylococcal parenteral infections (pharyngitis, otitis, impetigo) accompanied by diarrhoea (Tolentino, Ravasi and Durand, 1949). The third mechanism, which had been suggested by French workers (Lévesque, Bastin and Lafourcade, 1949), has seemed to us to be worthy of attention, since we have noticed that the presence of adsorbent foods in the intestine does not always prevent diarrhoea, as should be the case if the only mechanism were that of the irritative action of the toxins present in the intestinal lumen (Tolentino, 1949). We have thus reached the hypothesis that some enteritic forms may be caused by enterotoxic staphylococci with a mechanism acting on the central nervous system. We have carried out an investigation on sucklings suffering from gastro-enteritis with pharyngitis by isolating the pharyngeal staphylococci on Buttiaux and Brogniart's (1947) culture media, and by testing the enterotoxic activity of a filtrate of the culture from Dolman and Wilson's (1938) medium in kittens. The first positive case was reported by Tolentino and Ravasi in 1950. Four similar cases have since been studied (Tolentino and Ravasi, 1951). We have found enterotoxic staphylococci in the pharynx of 2% of healthy children and of 26% of children suffering from gastro-enteritis with pharyngitis. Non-enterotoxic staphylococci were isolated in 50% of healthy children and in 37% of infants with gastro-enteritis (Fig. 4).

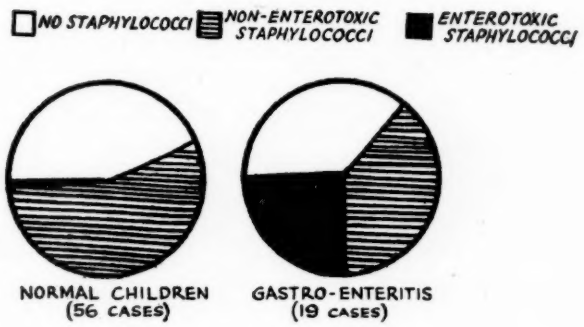

FIG. 4.

In those cases of gastro-enteritis with pharyngitis, where the staphylococcus is not found, the cause may be different, presumably being due to a virus, but it is interesting that in as many as 26% of our cases the staphylococcus was responsible for both pharyngitic and gastro-enteritic symptoms. The suckling appears to be more sensitive than the adult to the action of the enterotoxin, since for enteritic symptoms to be produced in the latter it seems necessary for them to have eaten food contaminated by a carrier of infection (Wilson, 1938). It must also be noted that, unlike the strains isolated from contaminated food, the strains isolated from children's pharynxes lose their enterotoxin-producing capacity in a few weeks:

it seems, therefore, that this feature is less consistently connected with their type.

The mode of action of the enterotoxin has been shown by the administration of the toxin in large doses to animals (Tolentino and Bellieni, 1951). These workers produced lesions of the central nervous system, diapedetic haemorrhages (Fig. 5) and degenerate lesions of the nerve centres (Fig. 6) namely, lysis of the tigroid, pyknosis of the nuclei, and pseudo-neuronophagia. On injecting large doses of the toxin, the animal, instead of showing the classical symptomatology of diarrhoea and vomiting, merely exhibited a neurological symptomatology characterized by convulsions, opisthotonus, ataxia, hallucinations, and coma and death within 24 hours. It therefore appears possible that enterotoxin acts through a neurotoxic mechanism and that both vomiting and diarrhoea may also be originated by a central mechanism. Not only does such an assumption imply a central nervous origin for these cases of gastro-enteritic symptomatology, but it also supports the suggestion that even some cases of toxicosis, such as the encephalitic type with scanty gastro-enteritic signs, may have a staphylococcal origin.

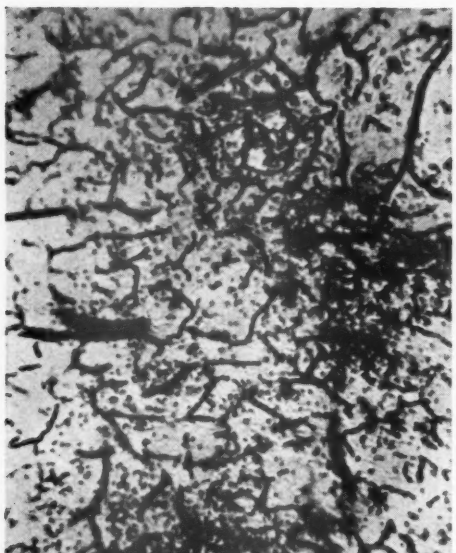

FIG. 5.—Photomicrograph showing diapedetic haemorrhages in the central nervous system in experimental animals (Pickworth's method × 55).

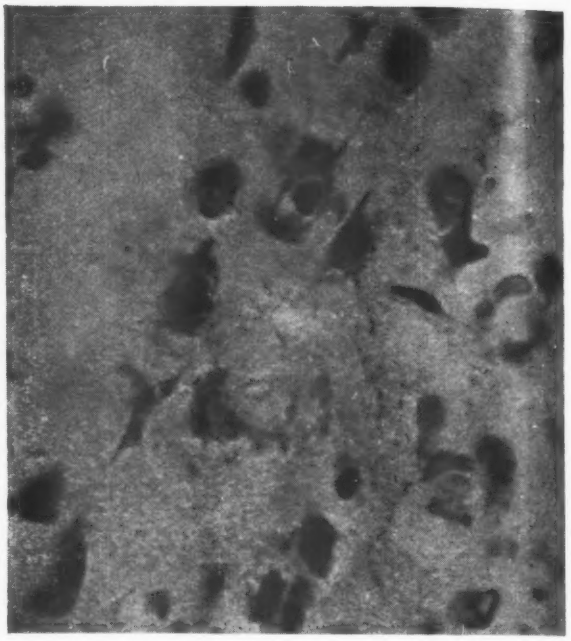

FIG. 6.—Photomicrograph showing degenerate lesions of the nerve centres (Nissl × 600).

REFERENCES

Buttiaux, R. and Brogniart, R. (1947). *Ann. Inst. Pasteur*, **73,** 830.

D'Alessandro, G. and Burgio, G. R. (1945). *G. Med.*, **2,** fasc. 2-3.

Dolman, C. E. and Wilson, R. J. (1938). *J. Immunol.*, **35,** 13.

Hurtado, F. and Aballi, A. J. (1949). *2nd Congr. Panam. Ped.* Mexico.

Lévesque, J., Bastin, R. and Lafourcade, J. (1949). *XII° Congr. Ped. Langue Franc.* Paris.

Light, J. S. and Hodes, H. L. (1949). *J. exp. Med.*, **90,** 113.

Nelson, W. (1950). In *Mitchel-Nelson Textbook of Pediatrics.* Philadelphia.

Tolentino, P. Unpublished data.

—— (1949). *XX° Congr. Ital. Ped.* Taormina.

—— (1950). *Ann. paediat. (Basel)*, **175,** 201.

—— and Bellieni, G. (1951). *Pediatria (Napoli)*, **59,** 309.

—— and Ravasi, R. M. (1950). *Minerva pediat. (Torino)*, **2,** 172,

——, —— (in press).

——, —— and Durand, P. (1949). *XX° Congr. Ital. Ped.* Taormina.

Wilson, R. J. (1938). *Canad. publ. Hlth. J.*, **29,** 329.

METHYL TESTOSTERONE IN PREMATURE INFANTS

BY

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It is an established fact that testosterone compounds cause a reduction in urinary nitrogen excretion which affects mainly the urea fraction. The faecal nitrogen excretion remains unaltered, leading to a nitrogen retention in the tissues. The haemoglobin, plasma protein, non-protein nitrogen and urea concentrations in the blood are unchanged. The urinary sodium, chloride, potassium and phosphorus are reduced. The net result is a gain in weight due to water retained by the electrolytes and protein. The gain exceeds any possible increase accounted for by enlargement of genital tissue and represents true somatic growth. After testosterone is discontinued there is a rapid loss of water, sodium and chloride from the body, potassium and phosphorus are slowly excreted, but nitrogen remains in the tissues for some weeks. Similar results have been observed in eunuchoids and in normal controls of both sexes (Kenyon, Knowlton and Sandiford, 1944; Kenyon, Knowlton, Sandiford, Koch and Lotwin, 1940).

This property of testosterone to promote nitrogen retention suggests a possible use in the treatment of premature infants to promote a more rapid weight gain. Several reports of its use in this connexion have been published in the American literature. Shelton and Varden (1946) treated 15 premature infants with birth weights of less than 1,920 g. (4 lb.) with methyl testosterone (2·5 mg. 12-hourly for three to seven weeks). Their initial weight losses were reported to be minimal and subsequent weight gain and vigour were initiated early. No undesirable side-effects were noted. In further papers (Shelton, Varden and Mark, 1947; Shelton and Mark, 1948) 74 prematures were divided into three groups. Twenty were used as controls, 30 received methyl testosterone, 5 mg. daily in propylene glycol, and 24 were given 4 mg. of testosterone propionate daily by intramuscular injection. Treatment was started at 12 hours and continued for three weeks. The cases were further sub-divided according to birth weight, 1,000-1,500 g. and 1,500-2,000 g. Of those with the lower birth weights the controls took an average of 14·7 days to regain their birth weight, those receiving methyl testosterone averaged nine days, and those receiving testosterone propionate 7·5 days. Of the cases with birth weights of 1,500-2,000 g., the controls took an average of 11·9 days to regain their birth weight, those on methyl testosterone 7·8 days and those on testosterone propionate 9·8 days. The treated cases also reached the weight of 2,500 g. significantly earlier than the controls. Four sets of twins were also investigated. In three sets the larger twin acted as control and the smaller twin received testosterone. In all four sets the treated twin was the first to reach both birth weight and 2,500 g. No difference between the two compounds used was noted apart from the greater accuracy of dosage possible with the intramuscular testosterone propionate, and no side effects were seen. Tittle (1949) reported 18 premature infants with birth weights ranging from 3 lb. to 4 lb. 13 oz. These were given 2·5 mg. testosterone 12-hourly from 24 hours until 5 lb. was reached. These cases were compared with infants born during the previous year of comparable birth weight. The treated cases showed a 45% decrease in the number of days taken to regain their birth weight and a 32% advantage in reaching 5 lb.

Hardy and Wilkins (1949), however, found that 26 infants given 2·5 mg. of methyl testosterone 12-hourly starting between the seventh and tenth day and continuing for four weeks showed no significant advantage over 26 control cases with a similar feeding regime. Two of these cases developed moderate enlargement of the penis and several females had transient enlargement of the clitoris. Seitchik and Agerty (1950) treated 27 premature infants with birth weights of 1·3 to 2·3 kg. with 2·5 mg. of methyl testosterone 12-hourly and compared them with 30 controls. The percentage of nitrogen retained was slightly higher in the treated cases, but there was no marked difference in the time taken to regain birth weight, to reach 2·5 kg., or in the percentage of birth weight attained during the period of study in the two groups. Reilly and Earle (1951) found no difference between the progress of 25 premature infants given 5 mg. methyl testosterone in propylene glycol daily and 25 control prematures. Therapy started between the fourth and eighteenth days

(average tenth day) and was continued for an average of 24 days.

The Present Investigation

The present investigation, which lasted for one year, was undertaken to determine (1) if methyl testosterone had any effect on the rate of weight gain in premature infants, and (2) if the effect of methyl testosterone was enhanced by simultaneous high protein feeding.

The investigation was conducted at two maternity hospitals and the cases were divided as follows:

Hospital X (General Lying-In Hospital). All infants were divided into three groups according to birth weight. Group (1) birth weight 4 lb. 8 oz.-5 lb. 8 oz.; Group (2) birth weight 3 lb. 8 oz.-4 lb. 7 oz.; Group (3) birth weight under 3 lb. 8 oz.

Alternate cases were further subdivided into Groups A and B. Group A received 'casinal', 1 g. per lb. of birth weight per day, from the third or fourth day according to when feeding began. Group B received 'casinal' as in Group A together with methyl testosterone (Ciba) 5 mg. daily by mouth. This was continued until the infant was discharged, or for 28 days in cases where prolonged hospital treatment was required. These cases were compared with premature infants born in the same unit in 1948-49, and subject to the same feeding methods.

Hospital Y (Annie McCall Maternity Hospital). Cases were divided into similar weight groups and further subdivided into Groups C and D. Group C acted as controls. Group D received methyl testosterone, 5 mg. by mouth, daily from the first or second day. The testosterone was given during the stay in hospital or for 28 days as in Hospital X.

At both hospitals the feeding regime was the same. Breast milk was fed whenever possible. Where this was not possible half cream Cow and Gate made up to 20 calories per ounce was used. Seven calories per pound of birth weight were given on the first day of feeding, and this was increased in multiples of seven calories up to 50 calories per pound on the seventh day. Further increases over 50 calories per pound were made when tolerated. Breast feeding was initiated early in some cases, in others various forms of hand feeding were employed as indicated by the vigour of the infant. No subcutaneous fluid was given in any case. In all cases except 10 in Groups 2 and 3 feeding was started on the first or second day of life. In the other 10 feeding began on the third day. Vitamins A and D were added on the tenth day and vitamin C on the fourteenth. The criteria of progress adopted were the number of days taken to regain birth weight, and the weight gain over and above birth weight at the age of 1 month.

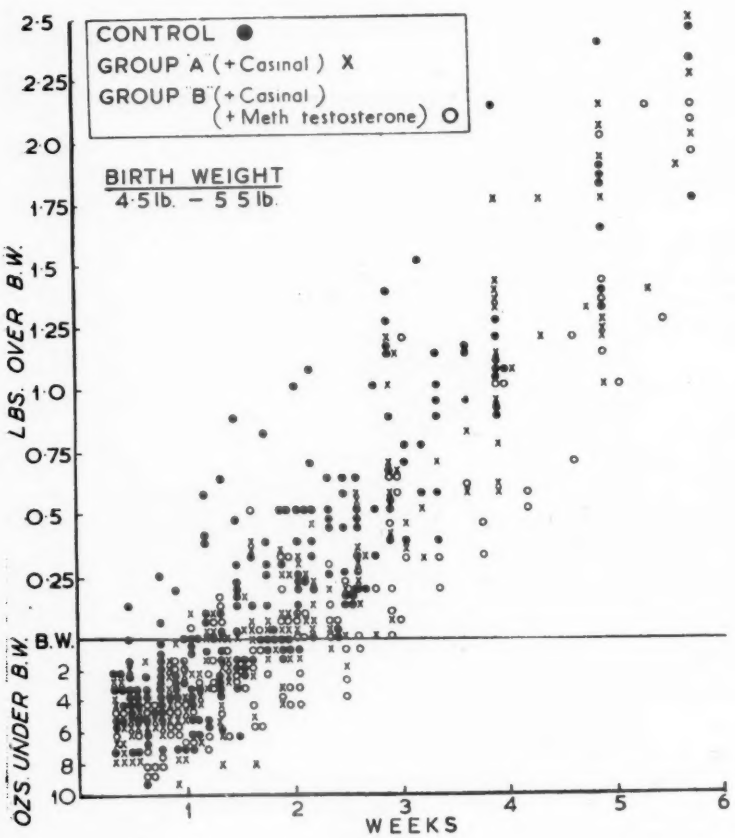

FIG. 1.

At Hospital X the minimum number of days of treatment was six days (one case), the maximum 28 days, and the average 15 days. At Hospital Y the minimum number of days in which testosterone was given was 10, the maximum 28 and the average 17·6. All cases at this hospital were started on feeds on the first or second day of life.

Results

The days taken to regain birth weight in Groups 1 and 2 at both hospitals are shown in Tables 1 and 2. The average time taken for treated cases to regain birth weight was slightly longer than in the controls,

but the differences are not conclusive. The number of Group 2 cases seen at Hospital Y are too small to draw any conclusions and no Group 3 cases were seen at this hospital.

The Group 3 cases at Hospital X were all Group B and the results are given in Table 3. The two Group A cases both died during the first fortnight, one from congenital heart disease and one from bronchopneumonia, and they are therefore excluded from this series.

Figs. 1 and 2 show the weights of control and treated cases at Hospital X plotted at various ages. No significant difference between the two is apparent. Fig. 3 shows similar scatter for both Group 1 and 2 cases from Hospital Y.

Table 4 shows the gain over birth weight attained at 1 month of age at Hospital X. Not all the original cases returned for follow-up at this age, so that the numbers compared are less than those treated in the hospital.

Results for cases from Hospital Y are given in Table 5.

The average weight gain in all treated cases is slightly lower than in the controls in all weight groups.

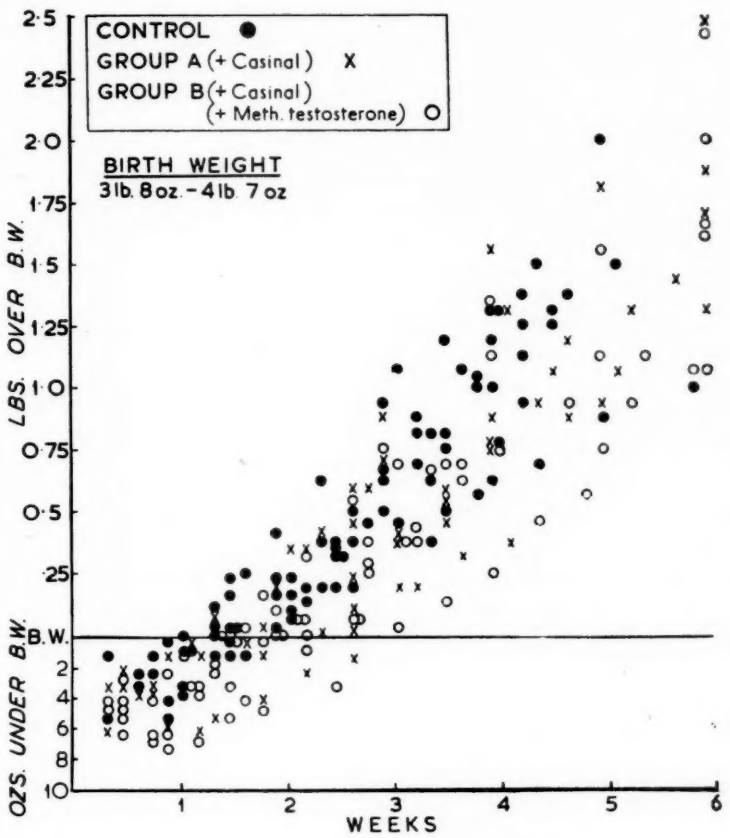

FIG. 2.

TABLE 1
DAYS TAKEN TO REGAIN BIRTH WEIGHT AT HOSPITAL X

	Group 1			Group 2		
	Control	A	B	Control	A	B
No. of Cases	37	20	14	10	6	7
Minimum days to regain birth weight	0	8	7	8	8	10
Maximum days to regain birth weight	17	19	20	13	21	21
Average days to regain birth weight	10·8	11·7	13·3	10·5	14·1	14·2

TABLE 2
DAYS TAKEN TO REGAIN BIRTH WEIGHT AT HOSPITAL Y

	Group 1		Group 2	
	Group C	Group D	Group C	Group D
No. of Cases	12	8	3	2
Minimum days to regain birth weight	0	5	5	12
Maximum days to regain birth weight	16	17	14	15
Average days to regain birth weight	8·8	9·1	8	15·5

Table 3 shows the gain above birth weight of Group 3 cases at 1 month of age, and where possible at 2 and 3 months. No marked difference between control and treated cases is demonstrated.

Throughout the investigation a careful watch was kept for side-effects. The only one noted was a transient enlargement of the clitoris in two cases at Hospital Y. No oedema was seen in any case following the administration of methyl testosterone with or without ' casinal '.

Discussion

In agreement with other observers, we found no adverse effects of the use of methyl testosterone, and the substance appears safe for administration to premature infants in the dosage employed. Since testosterone is known to accelerate epiphyseal union Shelton and Mark (1948) radiographed the long bones of all infants during treatment and again at the end of one year, but no radiological differences were observed between control and treated cases. Kenyon, Knowlton and Sandiford

TABLE 3

WEIGHT GAINS OF GROUP 3 CASES AT HOSPITAL X

	Birth Weight	Days to Regain Birth Weight	Weight Gain		
			1 month	2 months	3 months
	lb. oz.		lb. oz.	lb. oz.	lb. oz.
Control	2 7	23	3	2 0	2 8
Control	3 6	14	1 0	1 14	3 8
Treated	3 6	14	15	2 3	—
Treated	3 10	20	6	—	—
Treated	2 10	25	1½	1 3	4 5

TABLE 4

WEIGHT GAINS AT 1 MONTH OF AGE AT HOSPITAL X

	Group 1			Group 2		
	Control	A	B	Control	A	B
No. of Cases	15	15	11	9	6	7
	lb. oz.	lb. oz.	lb. oz.	lb. oz.	lb. oz.	lb. oz.
Maximum weight gain	2 3	1 15	1 10	1 6	1 10	1 6
Minimum weight gain	8	10	7	10	8	5
Average weight gain	1 4½	1 3½	13½	1 1	1 0	13½

(1944) state that epiphyseal closure is not readily induced and that prolonged and heavy dosage is necessary to produce it.

As no oedema was seen in cases following the administration of testosterone, it appears that the nitrogen retention induced by this substance does not lead to water retention in the form of clinical oedema. If water retention is responsible for any gain in weight it must be utilized for true somatic growth. No investigations to demonstrate increased nitrogen retention were made in this series, but the dosage of methyl testosterone was the same as in cases where this had been shown (Seitchik and Agerty, 1950) so that it was unlikely that inadequate dosage was responsible for our failure to obtain weight gain. Seitchik and Agerty, however, question whether adequately nourished prematures respond to the theoretical growth stimulation of testosterone, and are supported by Beattie (personal communication) who found that adults only responded by weight increase and marked nitrogen retention where previous physiological stresses, i.e. infections, trauma, etc., were a prominent feature. Normal adult controls failed to show any appreciable results when treated with testosterone. Shelton and Varden (1946) and Tittle (1949) started testosterone during the first 24 hours and claimed significant results, whereas Hardy and Wilkins (1949) began treatment on the seventh to tenth day and were unable to show that it accelerated growth. Our cases at Hospital Y started testosterone on the first or second day and those at Hospital X on the third or fourth day. We feel that it is unlikely that a delay of 24 to 48 hours in starting therapy has made a significant difference to our results. The duration of treatment in this series was less than in other reported cases, but once an infant was sufficiently established to leave hospital there seemed little point in continuing testosterone, and we felt that the uncertainties of dosage inherent in domiciliary administration would

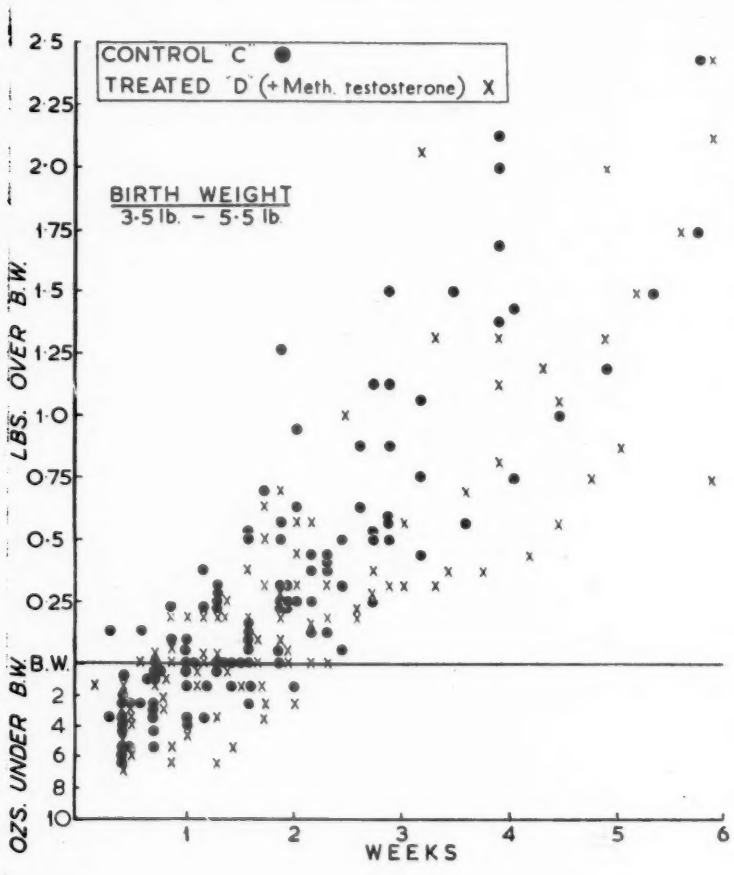

FIG. 3.

TABLE 5
WEIGHT GAIN AT 1 MONTH OF AGE AT HOSPITAL Y

	Group 1		Group 2	
	Control	Treated	Control	Treated
No. of Cases	6	6	3	2
	lb. oz.	lb. oz.	lb. oz.	oz.
Maximum weight gain ..	2 2	2 8	2 0	14
Minimum weight gain ..	1 1	14	13	6
Average weight gain ..	1 11	1 11	1 8	10

have made further treatment valueless from the point of view of a controlled investigation.

We were anxious to ascertain if the addition of protein to standard feeds would in any way enhance the action of testosterone and the group of cases receiving 'casinal' alone was included in order to prove that high protein feeding itself was not responsible for any accelerated weight gain.

Consideration of the results from the two hospitals makes it plain that the simultaneous administration of protein and testosterone has no advantage. This is not in accordance with the work of Earle (1951) who noted appreciable difference in weight gain and shorter hospital stay in 13 premature negro infants who were given methyl testosterone, 5 mg. daily together with 100-150 ml. plasma orally a day, until they reached the weight of 2,722 g. These were compared with a control series receiving similar routine treatment and feeding.

Summary

Fifty premature infants were divided into two groups. Twenty-six received 'casinal', 1 g. per lb. birth weight daily, starting on the third or fourth day. Twenty-four received the same dose of 'casinal' together with 5 mg. methyl testosterone daily by mouth. These were compared with 49 controls from the previous year.

Twenty-five premature infants from another hospital were divided into two groups, 10 receiving 5 mg. methyl testosterone from the first or second day, and 15 were controls.

All groups were further subdivided according to birth weight.

No significant difference in the time taken to regain birth weight or the amount of weight gained over birth weight at 1 month was noted between the treated cases and the controls in any weight group.

No side-effects were noticed as a result of treatment apart from transient enlargement of the clitoris in two cases.

We think it unlikely that the normal adequately nourished premature infant responds to the growth stimulus of testosterone, and in our opinion this hormone is of no value in the rearing of healthy premature babies.

We wish to thank the resident medical officers and the nursing staff of the hospitals concerned for their unfailing co-operation throughout the investigation. We also wish to thank Professor John Beattie for his helpful criticism.

REFERENCES

Beattie, J. (1951). Personal communication.
Earle, A. M. (1950). *J. Pediat.*, **36**, 87.
Hardy, J. and Wilkins, L. (1949). *Ibid.*, **34**, 439.
Kenyon, A. T., Knowlton, K. and Sandiford, I. (1944). *Ann. intern. Med.*, **20**, 632.
——, ——, ——, Koch, F. C. and Lotwin, G. (1940). *Endocrinology*, **26**, 26.
Reilly, W. A. and Earle, A. M. (1951). *Amer. J. Dis. Child.*, **82**, 323.
Seitchik, J. N. and Agerty, H. A. (1950). *Pediatrics*, **5**, 200.
Shelton, E. K. and Mark, J. S. (1948). *Calif. Med.*, **69**, 339.
—— and Varden, A. E. (1946). *J. clin. Endocr.*, **6**, 812.
——, —— and Mark, J. S. (1947). *Ibid.*, **7**, 708.
Tittle, G. A. (1949). *Tex. St. J. Med.*, **45**, 563.

THE INCIDENCE AND SIGNIFICANCE OF BREAST FEEDING IN INFANTS ADMITTED TO HOSPITAL

BY

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Most doctors believe that breast fed babies do better than those artificially fed, but this is difficult to prove, especially where the standard of living is high. Thus, Douglas (1950) followed up 4,848 of the infants whose early history had been reported in *Maternity in Great Britain* 1946, and found few striking differences between those who had been breast and bottle fed; the breast fed babies had a slightly lower mortality, though the difference was not statistically significant, and they had fewer attacks of pneumonia and of diarrhoea in the early months of life. On the other hand Naish (1951) found that in her practice bottle fed babies in all social classes were more often ill than breast fed ones, requiring on an average more than four times as many visits per baby during the first year of life. Crosse (1951) compared the mortality in breast and bottle fed premature and full term babies in Birmingham. Among 1,061 babies of birth weight 5½ lb. or less, the mortality between 1 and 6 months of age varied from 0·8% (wholly breast fed) to 5·6% (wholly bottle fed). The corresponding figures for 2,717 mature babies were 0·4% and 1·4%. The smallest babies had the highest mortality rates, but in each birth weight group the breast fed babies were more likely to survive. In a poor district of Liverpool, Robinson (1951) studied 3,266 babies attending a welfare clinic during the years 1936-1942; wholly breast fed babies had a mortality of 10·2 per 1,000, while 57·3 per 1,000 of those never breast fed died. The corresponding morbidity rates were 223·4 and 573·7 per 1,000. These figures are comparable with those of Grulee, Sanford and Herron (1934), who found that the mortality of bottle fed babies in the poorest parts of Chicago was over four times that of breast fed babies, and the morbidity twice as high. It is clear that the dangers of bottle feeding are greatest in poor homes and among premature babies.

The reported feeding histories of infants admitted to hospital show that sufferers from infantile diarrhoea have generally been weaned early (e.g. Smellie, 1939; Campbell and Cunningham, 1941; Gairdner, 1945). About other illnesses there is less agreement, although a comparatively high incidence of bottle feeding in infants with various infections has generally been reported (e.g. Ebbs and Mulligan, 1942; Deeny and Murdock, 1944). It may be objected that such figures are unconvincing, for the knowledge of the incidence of breast feeding in the population at risk is meagre.

In this paper the feeding history of infants admitted to hospital for infective illnesses is compared with that of infants admitted with other conditions.

Material

All infants aged 16 weeks or under admitted to Birmingham Children's Hospital during 1949 and 1950 were included in the investigation (1,044 admissions). Each case was classified as 'clean' or 'infected', according to the disease for which the child was admitted; if several conditions were present only the most important was considered. Clean cases were subdivided into 'pyloric stenosis' and 'other clean', and 'infected' into upper and lower respiratory tract infections, diarrhoea and vomiting, and other infections (pyelitis, meningitis, skin infections, etc.).

Results

More clean cases than infected ones were breast fed on admission, especially among those aged 5-8 and 9-12 weeks, where the difference is statistically significant (Table 1 and Fig. 1).

The clean cases, however, included a large proportion where breast feeding would have been

TABLE 1

ANALYSIS OF CLEAN AND INFECTED CASES IN RELATION TO BREAST FEEDING

Age in weeks		0–1	1–4	5–8	9–12	13–16
All clean (690 cases)	No.	177	181	179	105	48
	B.F.*	41	86	42	13	4
	B.F.%	22·4	47·5	23·5	12·4	8·5
All infected (354 cases)	No.	18	81	100	84	71
	B.F.	2	29	6	2	7
	B.F.%	11	34	6	2·5	9
S.E. of difference		8·7	6·6	5·7	4·4	—

* B.F. = breast-fed.

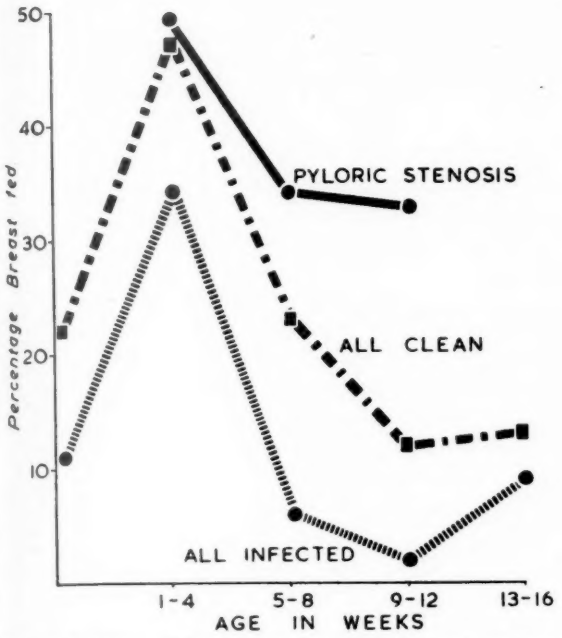

FIG. 1.—Incidence of breast feeding in pyloric stenosis, all clean and infected cases.

difficult or impossible, such as cases of harelip and prematurity, and numbers of cases of ' feeding difficulties ' which were mostly bottle fed. The feeding histories of ' infected ' cases have, therefore, been compared with those of babies with pyloric stenosis, a more homogeneous control group. Table 2 shows that these babies were much more

TABLE 2

FEEDING HISTORIES OF INFECTED AND PYLORIC STENOSIS CASES COMPARED

Age in weeks		0–1	1–4	5–8	9–12
Pyloric stenosis (201 cases)	No.	2	85	90	24
	B.F.	2	42	31	8
	B.F.%	—	49	34·5	33
All infections (283 cases)	No.	18	81	100	84
	B.F.	2	29	6	2
	B.F.%	11	34	6	2·5
S.E. of difference		—	7·2	5·8	6·7

often breast fed than infected cases in the same age groups; the difference is greatest at ages 5-8 and 9-12 weeks, but is also significant at ages 1-4 weeks.

When the different groups of infection are considered separately it will be seen that scarcely any babies with diarrhoea and vomiting or with upper respiratory tract infections (including otitis media and mastoiditis) were breast fed. Between the ages of 5 and 12 weeks there were no breast fed babies with such infections. Babies with lower respiratory and other infections were more often breast fed, though less frequently than clean cases (Table 3 and Fig. 2).

TABLE 3

RELATION BETWEEN BREAST FEEDING AND CERTAIN DISORDERS

Age in weeks		0–1	1–4	5–8	9–12	13–16
Pylorics (201 cases)	Cases	2	85	90	24	0
	B.F.*	2	42	31	8	0
	B.F.%	—	49	34·5	33	—
Other clean (489 cases)	Cases	175	96	89	81	48
	B.F.	39	44	11	5	4
	B.F.%	22·5	45·7	12·4	6·2	8·3
Upper respiratory tract infections (89 cases)	Cases	3	19	25	20	22
	B.F.	0	9	0	0	1
	B.F.%	—	47	—	—	4·5
Lower respiratory tract infections (60 cases)	Cases	3	11	23	10	13
	B.F.	1	4	4	1	1
	B.F.%	33	36	17	10	7·7
Diarrhoea and vomiting (115 cases)	Cases	0	19	36	39	21
	B.F.	0	2	0	0	1
	B.F.%	—	10·5	—	—	4·5
Other infections (90 cases)	Cases	12	32	16	15	15
	B.F.	1	14	2	1	4
	B.F.%	8·3	44	12·5	6·1	2·6
All infections (354 cases)	Cases	18	81	100	84	71
	B.F.	2	29	6	2	7
	B.F.%	11	34	6	2·5	9
All clean (690 cases)	Cases	177	181	179	105	48
	B.F.	39	86	42	13	4
	B.F.%	22	47·5	23·5	12·5	8·3

* B.F. = Breast fed on admission.

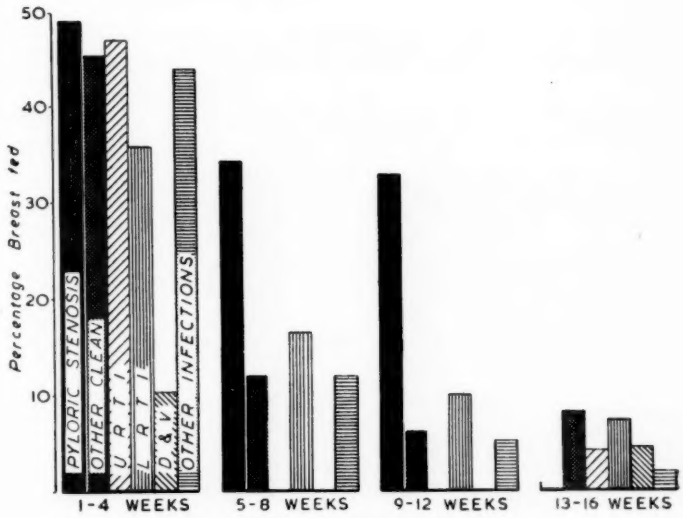

FIG. 2.—Incidence of breast feeding by diagnosis.

The child's place in the family was also studied. As might be expected more children with infections had older brothers and sisters, but the difference was not significant, nor did the incidence of breast feeding in the various disease groups vary with place in family.

Discussion

Assuming that the 201 cases of pyloric stenosis and the 354 infected cases were equally representative samples of the infant population served by the hospital, these figures indicate that breast fed infants are less likely than bottle fed ones to suffer from infections, especially of the upper respiratory and alimentary tracts. The two samples are not comparable, however, for at least two obvious reasons. (1) The pyloric stenosis group included more babies whose parents were of social classes 1 and 2 (24·6%) than the infected group (7%). This was probably because better-off parents are unwilling to have their babies admitted to hospital, except when an operation is necessary. The breast-feeding record of social classes 1 and 2 is better than that of classes 3-5 (Royal College of Obstetricians and Gynaecologists and Population Investigation Committee, 1948). In this small series, though rather more babies from better-off families were breast fed the differences were not statistically significant. (2) The admission of a breast fed infant means an upheaval in the home, involving as it does the admission of the mother too. Here, again, parents would be more willing to agree to the admission of mother and child for a dramatic illness like pyloric stenosis than, say, for otitis media.

It seems unlikely that such factors would cause so large a difference in the feeding histories as we have found; at ages 5-8 weeks the percentage of cases of pyloric stenosis breast fed on admission was nearly six times that of infected cases. Moreover, a considerable number of babies with pyloric stenosis had been recently weaned with the mistaken idea that the mother's milk was the cause of the vomiting; were it not for this still more of these would have been breast fed.

It is instructive that upper respiratory tract infection, like infantile diarrhoea, should be so largely confined to the bottle fed. As the bottle fed baby may be fed by numbers of different people it runs more risk of contracting an intercurrent infection, but impaired nutrition or delayed immunity may also play a part. This may be only surmise; the important point these figures emphasize is the considerably increased dangers of at least certain infections to which the artificially fed baby is exposed.

Summary

In 1,044 admissions of infants aged 16 weeks or under the method of feeding on admission was recorded.

Patients admitted with an infective illness were less often breast fed than those with non-infective conditions, and very much less often than those with pyloric stenosis. The difference was most marked at ages 5-12 weeks.

Babies with upper respiratory tract or gastro-intestinal infections were hardly ever breast fed on admission.

These figures suggest that breast fed babies are less likely to contract infections.

Certain qualifications to this statement are discussed.

The incidence of infections, etc., did not vary significantly with the child's place in family, nor did the incidence of breast feeding.

I wish to thank the consulting medical staff of the Children's Hospital, Birmingham, for the use of clinical notes and Professor J. M. Smellie for helpful advice and criticism. Part of the expenses of this investigation were defrayed from a grant from Messrs. Cow & Gate Ltd.

References

Campbell, R. M. and Cunningham, A. A. (1941). *Archives of Disease in Childhood*, **16**, 211.
Crosse, V. M. (1951). Personal communication.
Deeny, J. and Murdock, E. T. (1944). *Brit. med. J.*, **1**, 146.
Douglas, J. W. B. (1950). *J. Obstet. Gynaec. Brit. Emp.*, **57**, 335.
Ebbs, J. H. and Mulligan, F. (1942). *Archives of Disease in Childhood*, **17**, 217.
Gairdner, P. (1945). *Ibid.*, **20**, 22.
Grulee, C. G., Sanford, H. N. and Herron, P. H. (1934). *J. Amer. med. Ass.*, **103**, 735.
Naish, F. C. (1951). *Brit. med. J.*, **1**, 607.
Robinson, M. (1951). *Lancet*, **1**, 788.
Royal College of Obstetricians and Gynaecologists and Population Investigation Committee (1948). 'Maternity in Great Britain (1946).' London.
Smellie, J. M. (1939). *Lancet*, **1**, 969.

DENTAL CONDITIONS WITH ASSOCIATED SIGNS OF NUTRITIONAL DEFICIENCIES IN NEWFOUNDLAND CHILDREN

BY

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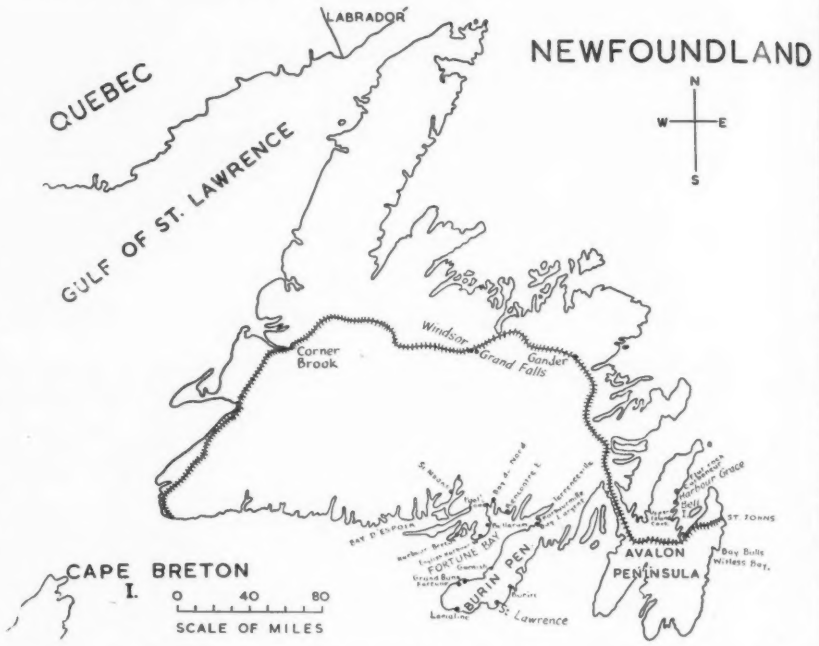
In undertaking this survey of Newfoundland children the primary concern was the incidence of dental disease, but an opportunity was taken of noting any signs suggestive of nutritional deficiencies which were observed during the examination of the individuals. The time of the visit (May-July, 1948) was chosen because it followed soon after the Newfoundland Government's latest measure designed to improve the standard of nutrition, namely that of adding 0·5% of bone meal to all flour before importation. This reinforcing of a staple article of diet was done to raise the low calcium intake, and, since it provides small amounts of fluorine as well as extra calcium, it might be expected to have some beneficial effect on the children's teeth. It was hoped that a subsequent survey might be made after the lapse of some years to estimate any alteration in the dental condition of the child population, especially of their caries susceptibility. For this latter reason the general results only will be given in this paper, leaving a more detailed assessment of the findings until such time as a future comparison may become available.

Newfoundland, at the mouth of the Gulf of St. Lawrence, has an area of 42,000 square miles and thus is a little smaller than England. At the last census in 1948 the population was 340,000, of which about one half was resident in the Avalon Peninsula. St. Johns, the capital, is the only town of any size (56,000) after which come the paper-mill company towns of Corner Brook and Grand Falls, having 10,500 and 7,300 inhabitants respectively, including their satellite settlements. The majority of the people live in small coastal fishing communities, of 200 to 800 individuals, many of which are relatively isolated for a large part of the year. The local name for these is 'outports'. On the Avalon Peninsula the outports have fairly good road communications, but others, on the south and north coasts particularly, have none except by sleigh in winter, while sea transport is often restricted by bad weather. The single track, narrow gauge railway provides an additional link between the main population centres as it traverses the island from St. Johns in the south-east to Port aux Basques in the south-west. A few roads have been built from some of the northern and western outports to the nearest railhead.

For many years it has been known that nutritional diseases such as beri-beri have been endemic in this part of the world (Little, 1912; Appleton, 1921; Aykroyd, 1930), and much has been written about the combination of circumstances which has in the past contributed to this state of affairs. The islanders have to contend with somewhat unfavourable climatic conditions which permit of only a short season for growing vegetable and livestock crops. In many places the soil is so scanty that potato patches are often only a few square yards in area, lying between rocks. Previously, almost the only occupation for the men was fishing, the start of which coincided with planting time, so that the 'gardens' were largely left to the women. Following a poor fishing season there was extreme poverty and the diets of the people, apart from the potatoes, cabbage and turnips grown in their own gardens, became restricted to cheap foodstuffs which could be stored for months, such as white flour (70% extraction), sugar, molasses, tea and margarine, to which salted fish (almost exclusively cod) and salted pork were added. Wild fruits, such as cranberries and bakeapples, were gathered and preserved for use in the winter. Very little use was made of dairy products owing to their scarcity, due again to the difficulty and expense of stall-feeding for many months of the year. Recently a number of important alternative occupations to fishing has grown up and there has been a period of comparative prosperity, but even so, this has not remedied the lack of dairy products very much. Livestock observed during my visits to the outports consisted of a few goats, an occasional cow, a few nondescript hens and some sheep. Many families still use no milk at all, apart from

a little of the much-diluted tinned product in their tea.

During the last eight years several groups of workers have visited the country to make sample surveys of the population for signs and symptoms of deficiency diseases and to assess the average dietary standards of the islanders (McDevitt, Dove, Dove, and Wright, 1944; Adamson* *et al.*, 1945; Metcoff *et al.*, 1945; Cuthbertson, 1947; Scobie, Burke and Stuart, 1949; Aykroyd* *et al.*, 1949). Though none of these surveys was specifically concerned with teeth, most workers commented on the great prevalence of dental decay and gingival disease. Indeed Aykroyd *et al.* (1949) consider that these have actually increased between 1944 and 1948.



Clinical Material

In planning this survey an attempt was made to sample all types of communities, but in order to obtain adequate numbers within the time limit of seven weeks, it was necessary to include the larger population centres such as the capital, St. Johns (56,000), the mining district of Bell Island (8,000) and the two paper-mill towns of Grand Falls (7,300) and Corner Brook (10,500) with their surrounding settlements (see map). Besides these larger aggregations of the population, three groups of outports were visited: (1) those on the Avalon Peninsula with roads connecting with St. Johns; (2) those on the Burin Peninsula having road communications with each other, but not at that time with the rest of the Island; (3) those of the south-west coast and Fortune Bay area which are isolated, except by boat, for some seven months of the year. It will be appreciated that the maintenance of an adequate health service to areas such as the Fortune Bay region presents special problems. In the case of dental treatment, the service was limited to extractions.

In this survey the children in all the larger centres of population were inspected at their schools, the arrangements having been kindly made by the education authorities. In more remote parts other methods had to be used, including house-to-house visits. The outports of the south-west coast were reached by sea in the hospital ship *Lady Anderson* generously made available by the Department of Public Health and Welfare.

The main part of the survey concerns the results of examining 804 5-year-old children and 595 14-year-olds. The younger age groups provided a picture of the deciduous dentition, while the older groups supplied information on the permanent teeth. Much smaller numbers of ' under 5s ' were seen in a few selected places, while in St. Lawrence (an endemic fluorosis area) all available children between 5 and 17 were inspected.

Methods

Dental Results. The dental results for each child were written on a separate chart, on which there were appropriate spaces for denoting which teeth were present; the amount of caries; the grade of Mellanby-type hypoplasia (Mellanby, M., 1923*a*), mottling, gingivitis and tartar. Notes on occlusion, attrition, staining and alignment were also included.

The mouth examination was made with an illuminated mirror and standard probes. The M-hypoplasia was first estimated, using a sharp, right-angled probe. Each tooth with a sufficiency of crown intact was graded for external structure by gently rubbing the buccal surface. A perfectly smooth surface was graded Hy_0 (no hypoplasia), while successive degrees of defective structure were classified $M\text{-}hy_1$, $M\text{-}hy_2$, $M\text{-}hy_3$. Any teeth with obvious enamel defects such as pitting, or the

* Adamson, J. D., Jolliffe, N., Kruse, H. D., Lowry, O. H., Moore, P. E., Platt, B. S., Sebrell, W. H., Tice, J. W., Tisdall, F. F., Wilder, R. M. and Zamecnik, P. C. (1945); Aykroyd, W. R., Jolliffe, N., Lowry, O. H., Moore, P. E., Sebrell, W. H., Shank, R. E., Tisdall, F. F., Wilder, R. M. and Zamecnik, P. C. (1949); Metcoff, J., Goldsmith, G. A., McQueeney, A. J., Dove, R. F., McDevitt, E., Dove, M. A. and Stare, F. J. (1945).

absence of enamel over small areas were classed together as ' gross hypoplasia ' which is the type usually described in textbooks. While every effort was made to keep this standard for hypoplasia comparable from day to day by referring to sets of graded shed and extracted teeth, it is felt that the examination of large groups of deciduous and permanent teeth, often in the same day, would tend to lower the standards for deciduous teeth, since these are on the whole so much smoother than their permanent successors. An average hypoplasia figure (A.H.F.) for groups of teeth was calculated by allotting one point to all teeth graded M-hy$_1$, two points to M-hy$_2$ teeth, three points to M-hy$_3$ teeth and dividing the sum of the points by the total number of teeth examined for structure.

The incidence of caries was estimated as carefully as possible, each lesion being recorded as 1, 2 or 3 according to the criteria adopted in previous surveys by May Mellanby and her colleagues (Mellanby and Coumoulos, 1944 and 1946; Mellanby and Mellanby, 1948). An average caries figure (A.C.F.) was worked out for groups of teeth on the same lines as the average hypoplasia figure. All missing *deciduous* canines and molars in the 5-year-olds were considered to have been extracted for caries, and were given a caries score of three. Missing incisors were considered to have been naturally shed, except where a reliable history of extraction was obtained from the mother. In the 14-year group all missing incisors and first molars were counted as extracted and were given a C_3 caries rating. A few absent canines, premolars and second molars were obviously unerupted and these were not counted as carious.

Gingivitis, Cheilosis and Other Signs Suggesting Nutritional Deficiency. Notes were made of any 5- or 14-year-old child showing gingivitis which was roughly classified as 0, 1, 2 or 3 depending on the extent of the condition and on the amount of hyperaemia and swelling of the interdigital papillae in each child (see Mellanby and Mellanby (1951) for details). Signs visible to the naked eye suggesting riboflavine, nicotinic acid or vitamin A deficiency were also recorded, but it must be emphasized that such signs were restricted to their appearance on the face and in the mouth of the child examined, and their significance is limited by the author's lack of previous experience in the clinical manifestations of the vitamin B deficiencies. The principal signs attributed to deficiency of one or more members of the vitamin B complex looked for were those mentioned by Sydenstricker (1941*a* and *b*) and illustrated in the Medical Survey of Nutrition in Newfoundland by Adamson *et al.* (1945) and in the recent re-survey of the same places by Aykroyd *et al.* (1949), namely those associated with ariboflavinosis such as cheilosis, angular fissuring of the mouth, magenta tongue and blepharitis and those associated with nicotinic acid insufficiency, giving tongue changes featuring hypertrophied or atrophied tongue papillae, fissuring, or oedema as evidenced by tooth impressions along the tongue margins. It was more difficult to be dogmatic about the skin and hair changes probably related to vitamin A deficiency, as so many of the children in the outports had obviously unbrushed hair, and the rather rough skin on their faces might be due, at least in part, to climatic conditions. Eye changes attributable to vitamin A deficiency were not observed in these young age groups.

Results

Caries in 5- and 14-year-old Groups. The general results for the prevalence of tooth decay in the Island, according to the locality, are given for the principal age groups of 5 and 14 years in Tables 1

TABLE 1
CARIES IN 5-YEAR-OLD NEWFOUNDLAND CHILDREN IN 1948

Locality	Principal Occupations	No. Children Examined	Percentage Mouths Caries-free	Total No. Teeth	Percentage Teeth Carious	†A.C.F.	D.M.F.‡ (per child)
St. Johns	Various urban	281	5·7	5,410	38·5	0·82	7·4
Bell Island	Iron ore mining	66	10·6	1,260	31·7	0·68	6·0
Inland towns: Corner Brook, Gander, Grand Falls, Windsor ..	Lumbering, paper manufacture, airport personnel	222	2·3	4,266	42·5	0·94	8·2
Outports: (1) Avalon Peninsula ..	Fishing, fish processing, small amount of manufacturing	70	10·0	1,362	40·2	0·83	7·8
(2) Burin Peninsula (excluding St. Lawrence) ..	Fishing and fish processing	67	10·5	1,299	35·8	0·72	6·9
St. Lawrence*	Fluorspar mining	17	70·5	340	6·2	0·12	1·2
(3) S.W. coast and Fortune Bay	Lumbering at St. Albans, fishing and some fish processing	81	4·9	1,593	40·7	0·83	8·0
Totals		804	7·2	15,530	38·5	0·82	7·4

* Area of endemic fluorosis. † Average caries figure = $\frac{\text{total caries figure}}{\text{no. of teeth examined}}$ ‡ D.M.F. = decayed, missing, filled.

TABLE 2A

CARIES IN 14-YEAR-OLD NEWFOUNDLAND CHILDREN IN 1948

Locality	Principal Occupations	No. Children Examined	Percentage Mouths Caries-free	Total No. Teeth	Teeth Carious (%)	Average Caries Figure	†D.M.F. per 100 Examined Mouths
St. Johns	Various urban	234	nil	6,392	36·0	0·78	985
Bell Island	Iron ore mining	61	3·0	1,692	25·1	0·54	698
Inland towns:							
Corner Brook, Gander, Grand Falls, Windsor ..	Lumbering, paper manufacture, airport personnel	115	nil	3,134	32·3	0·71	878
Outports:							
(1) Avalon Peninsula ..	Fishing and fish processing; small number of factory workers	70	1·4	1,928	30·2	0·66	832
(2) Burin Peninsula* ..	Fishing and fish processing	64	1·56	1,732	21·6	0·46	586
(3) S.W. coast and Fortune Bay ..	Lumbering at S. Albans; fishing and some fish processing	51	1·9	1,380	21·6	0·46	584
Totals	.. ..	595	0·8	16,258	30·7	0·66	839

* There were four individuals only in this age group resident in the fluorosis area of St. Lawrence. † D.M.F. = decayed, missing, filled.

and 2. A glance at these is sufficient to show that dental caries is very common. In the 5-year-old age group only 7·2% of children had no decayed teeth, while 38·5% of all deciduous teeth at this age were already attacked. This is equivalent to a 'decayed, missing, filled' rate (D.M.F.) per child of 7·4*. There was some slight variation in different geographical areas, the Bell Island children and those living in the Avalon and Burin Peninsula outports having rather less decay, while young children of St. Lawrence (an endemic fluorosis area) had a low incidence. For comparison with these Newfoundland results some figures are given in Table 2B for deciduous teeth in other groups of children.

Turning to the older group, children aged 14 showed less than 1% of mouths with no decay, while the percentage of permanent teeth attacked was 30·7, giving a D.M.F. of 8·39 per child. There was again some variation in different localities, Bell Island children and those of the Burin Peninsula and south-west coast area having less decay of their permanent teeth than those in the Avalon Peninsula outports, St. Johns or the paper-mill towns. The second part of Table 2B gives comparative results for other groups of children of approximately the same age. Many more comparative figures could be given, but from Tables 1, 2A and 2B it is evident that dental caries is almost universal in Newfoundland and the average number of teeth attacked is high in comparison with the U.S.A. or London, where the disease is considered all too common.

More detailed results for the various types of teeth will be given elsewhere, but at 5 years of age 46% of the deciduous upper central incisors and 71% and 76% of the lower first and second deciduous molars were already decayed. In the permanent teeth of the 14-year-olds, 31% of the upper central incisors, 79% of the upper 6-year-old molars, and 88% of the lower 6-year-old molars were carious.

Structure in 5- and 14-year-old Groups. In Table 3 will be found a synopsis of the results of examining both deciduous and the permanent teeth for surface structure (or M-type hypoplasia). From this it will be seen that among the deciduous teeth, only 27·8% were considered normal, the remaining 72·2% having some degree of surface roughness and giving an average hypoplasia figure of 1·06. The teeth of the upper jaw were definitely rougher than those of the lower, one reason for this probably being the tartar deposits commonly found on the upper molars, especially where little or no oral hygiene is practised. In fact 10% of the upper first molars and 25% of the upper second molars had readily visible tartar deposits.

Comparative results for tooth structure in London 5-year-olds showed 47% of all deciduous teeth in 1947 to have no M-type hypoplasia (Mellanby and Mellanby, 1948), while the results for a group of German children gave 50% with no M-hypoplasia (Mellanby, H., 1949). The average hypoplasia figure for the Newfoundland group was 1·06, for the London group 0·67 and for the German group 0·66. The deciduous teeth of the Newfoundland children may therefore be said to be of poorer structure than either of the other two groups.

In the permanent teeth (Table 3) only 8·7% could be said to be of smooth structure, while

* In assessing the D.M.F. for deciduous teeth, missing incisors were assumed to have been naturally shed, and were therefore not counted as 'missing due to extraction' except where a definite history was obtained.

some 91·3% had some degree of M-type hypoplasia. Again the upper jaw teeth are apparently of worse structure than the lower teeth, but considerable deposits of tartar on the upper first and sometimes the second molars, were common. Many of the '6-year-old molars' were so carious at this age, that insufficient crown surface remained for structure estimation.

In comparing the structure of the permanent teeth, of which only 8·7% were found to have no M-hypoplasia, with a group of London 14-year-olds (Mellanby and Mellanby, in press) some 23·6% of these latter in 1947 had smooth teeth, the average hypoplasia figure being 0·92 compared with 1·38 for the Newfoundland children. Therefore the permanent teeth of Newfoundland children also may be considered to be of poor average structure as assessed by this method.

Dental Caries and Tooth Structure in St. Lawrence Outport. In striking contrast to the mouths full of decayed teeth seen in all other parts of the island which were visited, the children of the outport called St. Lawrence, with a population of 800 according to the 1948 census, showed a high proportion of caries-free individuals. This settlement turned out to be an area of endemic fluorosis, where mottling of the permanent teeth was common. Unfortunately this fact was only discovered on arrival, so that the most had to be made of a half day's visit, which was all the time that the travelling schedule permitted. The water supply to one of the fluospar mines, for which accurate analyses

TABLE 2B

DENTAL CARIES IN GROUPS OF CHILDREN FROM VARIOUS PARTS OF THE WORLD

Place	Author	Date of Survey	No. of Children Examined	Age Group	Percentage of Individuals Caries-free	Percentage of Teeth Carious (D.M.F.* per 100 Teeth)	Average No. of Carious Teeth per Child (D.M.F. per Child)	Comments
London, England	Mellanby, M. and Mellanby, H. (1948)	1947	1,590	5	28·1	20·3	3·94	Children from State schools
Wuppertal, Germany	Mellanby, H. (1949)	1948	563	5	28·4	14·2	2·79	Children from State and private kindergartens
London, England	Mellanby, H. and Mellanby, M. (1950)	1949	692	5	14·9	26·7	4·66	Children from State schools
Hagerstown, U.S.A.	Knutson, Klein and Palmer (1940)	1938	327	6	not given	not given	5·16	Grade-school-children
Blaker and Fet, Norway	Toverud (1949)	1939 1947		4–5 4–5	1·0 28·0	47 21	— —	Rural areas Rural areas
U.S.A. (American Indians in Reserves)	Klein and Palmer (1937)	1929/33	1,300	14&15	23	11·1	3·12	Children distributed between 76 Reserves in 16 States
Isle of Lewis, Scotland	King (1940)	1937	185	13–15	30·8	8·5	2·2	Rural fishing communities
Hagerstown, Maryland, U.S.A.	Klein, Palmer and Knutson (1938)	1937	364	14	4·6	19·2	5·2	Typical east U.S.A. small town
Chicago, U.S.A.	Dean, Jay, Arnold and Elvove (1941)	1939	2,832	12–14	14·4 (average)	—	4·73 (average)	Average of 8 separate communities
Italy (four northern cities)	Schour and Massler (1947)	1945	475	11–15	53·4	—	1·05	Deciduous and permanent teeth included
Trinidad	King and Martin (1951)	1948	406	12–14	13·8	21·7	5·37	East Indian and Negro children
British Guiana	King and Martin (1951)	1948	100	12–14	13·0	18·4	4·91	East Indian and Negro children
South Shields, England	Weaver (1950)	1943 1949	500 500	12 12	25·8 50·6	— —	2·4 1·3	1·4 p.p.m. fluorine in water supply
North Sheilds, England	Weaver (1950)	1943 1949	500 500	12 12	4·8 26·4	— —	4·3 2·4	Negligible fluorine
Lucknow, India	Mellanby, M. and Shah (unpublished work)	1951	266	14	65·8	2·71	0·95	Pupils from colleges academies and schools
New Zealand	Fulton (1951)	1950	452	14	0·5	—	10·01	Urban and rural samples from State schools

* D.M.F.=decayed, missing, filled.

TABLE 3

SURFACE STRUCTURE OF CHILDREN'S TEETH IN NEWFOUNDLAND

	Total No. of Teeth							
	Including Gross and Unclassified	Excluding Gross and Unclassified	M-Hy$_0$* (%)	M-Hy$_1$ (%)	M-Hy$_2$ (%)	M-Hy$_3$ (%)	Gross Hypoplasia (%)	Average Hypoplasia Figure (%)
Deciduous teeth of 5-year-old group								
Upper jaw	7,078	7,061	17·5	42·5	36·2	3·6	0·2	1·26
Lower jaw	6,825	6,801	38·5	38·5	21·5	1·2	0·2	0·85
Total	13,903	13,862	27·8	40·5	29·0	2·4	0·2	1·06
Permanent teeth of 14-year-old group								
Upper jaw	6,516	6,391	4·9	30·4	50·4	2·5	1·8	1·51
Lower jaw	7,098	6,918	12·4	47·8	35·9	1·4	2·5	1·26
Total	13,614	13,309	8·7	44·3	42·9	1·9	2·2	1·38

* M-Hy$_0$=smooth surface; M-Hy$_1$=slightly rough; M-Hy$_2$=definitely rough; M-Hy$_3$=very rough.

were available, contained 1·5 p.p.m. of fluorine, and this well was also used by a number of families.

Seventeen 5-year-olds who had been born and reared in the district were examined, this number representing more than half the available children in the age-group; 12 of these were caries-free, the percentage of carious teeth over all being only 6·2, as against 38·5% for the rest of the Island, and the average caries figure 0·12, as compared with 0·82. Comparative figures for 5-year-olds in other areas of endemic fluorosis are given as 11% of teeth carious. The average caries figure is 0·21 in Maldon and district, England (Coumoulos, 1949), and 2·8% of teeth carious in 5-year-olds living in a New Jersey fluoride area (Klein, 1948). The caries experience of the St. Lawrence children is therefore of a similar order to that observed for the same age group in other fluorosis areas.

Of the older age group, only four life residents aged 14 could be found, so that an examination was next undertaken of all ages between 6 and 17. A total of 53 individuals aged 5 to 17 years of age were inspected. Since the numbers in separate age groups were small the general results are given in Table 4, divided up into deciduous and permanent teeth.

Only 9% of all deciduous teeth were carious, although some of the children were 8, 9 and 10 years of age. The average hypoplasia figure of 0·88 was also low, especially when it is realized that these children had a higher proportion of deciduous molars present than the 5-year group, (deciduous molars being on the average rougher on the external surface than incisors or canines).

Other workers, using the same standards for M-hypoplasia (King, 1944; Coumoulos, 1949), have reported that *deciduous* teeth in the Maldon fluorosis area of England tend to be of smooth external structure; thus they correlate the low incidence of dental decay with the prevalence of well-formed teeth.

Among the permanent teeth some 8·7% were found to be carious, with the low average caries figure of 0·17. It is not possible to compare this with the 30·7% of carious permanent teeth in the 14-year-old group for the rest of the Island, since many of the total number of permanent teeth from St. Lawrence came from children aged 7 to 13 years, and there was an undue proportion of incisors and newly-erupted premolars among their number. The high average hypoplasia figure in the permanent teeth is explained by the frequent presence of mottled ' pitting ', giving a rough external feeling to the probe. No fluorine analyses were available for the wells, other than the one supplying the mine, but in view of the low calcium intake, it is probable that 1·5 p.p.m. would be sufficient to cause a disfiguring grade of mottling in some individuals (Murray and Wilson, 1948).

The mode of life and the types of food eaten in St. Lawrence appeared to be very similar to that of other outports on the Burin Peninsula, except that better wages were earned, and this would tend to allow of a greater variety of foods, especially imported tinned products. The standard of living was then coming more into line with that enjoyed in the paper-mill towns, but in those latter, it

TABLE 4

CARIES AND STRUCTURE IN 53 ST. LAWRENCE CHILDREN AGED 5 TO 17 LIVING IN AN AREA OF ENDEMIC FLUOROSIS

	No. of Teeth Examined for Caries	Per-centage Carious	A.C.F.	No. of Teeth Examined for Structure	A.H.F.
Deciduous	670	9·0	0·19	634	0·88
Permanent	472	8·7	0·17	408	1·49

TABLE 5

CARIES IN NEWFOUNDLAND CHILDREN AGED 2 TO 5 YEARS

Age	No. Examined	Percentage of Children with Caries	Percentage of Teeth Carious
2	4	None	None
3	32	75·0	20·6
4	15	86·7	37·0
5	804	92·8	38·5

cannot be said to have decreased the dental caries (see Tables 1 and 2).

Caries in 2- to 4-year Age Groups. It was originally hoped that it would be possible to examine a reasonable number of pre-school-age children between 2 and 4 years, but this proved difficult to organize and was only done on a very limited scale in two localities, St. Johns and Fortune Bay (on the south-west coast). In all 51 were seen, 35 in St. Johns and 16 in south-coast outports. Even in these tiny children there were many with much decay in their teeth, and it will be seen (Table 5) that the proportion of children having decay rises sharply after the age of 2 years, as also does the percentage of decayed teeth.

Gingivitis, Cheilosis and Other Signs Suggestive of Nutritional Deficiencies. Gingivitis of the non-ulcerative type in man is regarded by many authorities as due to nutritional defects, but local factors such as tartar deposition, which in turn appears to be influenced by the physical properties of the food eaten, also play a part (King and Glover, 1945). In animals (dogs, rats), which have been maintained post-developmentally on diets adequate in other respects but low in vitamin A, the gum epithelium becomes abnormal in that it shows increased keratinization and a tendency for downgrowths to occur below the enamel cement junction (Mellanby, M., 1930*a* and *b*; 1939; King, 1936). Animals reared on a similar diet, or whose maternal parent was given the deficient diet before their birth, show the same changes much earlier (Mellanby, M., 1930*a*; 1939; Mellanby, H., 1939; 1941.) Deficiency of this vitamin in childhood might be expected to predispose a population to parodontal disease and it is more than likely that this state of affairs did exist in Newfoundland before the margarine of the islanders' diet was fortified with vitamin A in 1945. It is well recognized that scurvy in man is typically accompanied by gum changes, while swelling and hyperaemia of the gingivae have been produced experimentally in human volunteers as the result of ascorbic acid deprivation (Linghorne *et al.*,*

* Linghorne, W. J., McIntosh, W. G., Tice, J. W., Tisdall, F. F., McCreary, J. F., Drake, T. G. H., Greaves, A. V. and Johnstone, W. M.

TABLE 6

ASSOCIATION BETWEEN TARTAR DEPOSITS AND OCCURRENCE OF GINGIVITIS IN 5- AND 14-YEAR-OLD GROUPS

Grade of Tartar	Number of Children		Percentage of Children with Gingivitis		Average Gingivitis Figure	
	5-year Group	14-year Group	5-year Group	14-year Group	5-year Group	14-year Group
0 (none visible)	593	88	30·7	73·9	0·46	1·14
1 (slight)	104	113	44·2	68·1	0·61	1·21
2 (moderate)	71	274	59·2	79·2	0·93	1·43
3 (extensive)	16	120	(50·0)	92·5	(0·63)	2·08
Totals ..	784*	595	35·5	79·0	0·53	1·47

* A few of the 5-year-old charts could not be used for this Table as either the tartar or gingivitis assessment was in doubt.

1946). All the scientists who have carried out nutritional investigations in Newfoundland agree that the vitamin C intake has been and still is low, more especially in the spring. (McDevitt *et al.*, 1942; 1944; Adamson *et al.*, 1945; Metcoff *et al.*, 1945; Cuthbertson, 1947; Scobie, Burke and Stuart, 1949; Aykroyd *et al.*, 1949; Goldsmith, Darby, Steinkamp, Beam and McDevitt, 1950). In addition to the low vitamin C intake, which until recently was also accompanied by a low vitamin A content of the diet, there little oral hygiene is practised, except by those in the larger centres of population, and the food eaten is for the most part in an overcooked state, so that it is unlikely to have any particular cleansing properties. It seems from the foregoing remarks that gingival disease might be expected to be common among the inhabitants of the island, and this has been recorded by several observers as occurring among all ages of the population, but particularly among young adults, especially the women. On the basis of the rough classification referred to on page 275, 35·5% of the 5-year-olds and 78% of the 14-year-olds had some degree of gingival abnormality, the respective average gingivitis figures per child being 0·53 and 1·47. There was a definite variation in the incidence in different localities, the Burin Peninsula and south-west coast children having once again the highest number of individuals affected (Table 7). Aykroyd *et al.* (1949), in a sample of the population aged 0-89 years, report an increased incidence of gingivitis in 1948 over their 1944 survey, and conclude from this that the average vitamin C intake is still much below the optimum.

The 5-year-old group did not show an unduly high gingivitis incidence when compared with

TABLE 7

INCIDENCE OF GINGIVITIS, CHEILOSIS AND OTHER CONDITIONS SUGGESTIVE OF NUTRITIONAL DEFICIENCIES IN 5- AND 14-YEAR-AGE GROUPS

Locality	No. of Children	Percentage with Gingivitis	Cheilosis and Angular Fissures	Blepharitis	Tongue Changes (Papillae, Fissuring or Oedema)	Rough Skin on Face
St. Johns:						
5-year group	281	21·7	2 cases	2 cases	2 cases	18 cases (6·4%)
14-year group	234	82·1	—	—	—	2 cases
Bell Island:						
5-year group	66	21·2	—	3 cases	1 case	6 cases (9·1%)
14-year group	61	62·5	1 case	1 case	1 case	3 cases (4·9%)
Inland towns:						
5-year group	222	41·0	5 cases (2·3%)	—	—	20 cases (9·0%)
14-year group	115	77·5	1 case	2 cases	5 cases (4·3%)	—
Outports:						
(1) Avalon Peninsula						
5-year group ..	70	47·2	4 cases	3 cases	—	3 cases
14-year group ..	70	81·5	5 cases (7·1%)	1 case	—	1 case
(2) Burin Peninsula						
5-year group ..	84	59·5	13 cases (15·5%)	—	5 cases (5·9%)	24 cases (28·6%)
14-year group ..	64	82·3	16 cases (25·0%)	3 cases	5 cases (7·8%)	6 cases (9·4%)
(3) S.W. Coast and Fortune Bay						
5-year group ..	81	55·5	33 cases (40·7%)	7 cases	33 cases (40·7%)	17 cases (21·0%)
14-year group ..	51	80·5	14 cases (27·5%)	2 cases	26 cases (51·0%)	8 cases (15·7%)

London children of the same age, who in 1947 had 49% of individuals affected (Mellanby and Mellanby, unpublished work). It is probable that in Newfoundland the underlying developmental predisposition would affect the older age groups to a greater extent, since those children aged 5 in 1948 (the date of this survey) should have been getting more vitamin A at a critical time in the development of the gingivae than either the older children or adults had received.

The 14-year-old group showed a slightly greater incidence and extent of gingivitis than did London school children of the same age in 1947 (Mellanby and Mellanby, 1952) when 74% of the individuals were affected and the average gingivitis figure per child was 1·26. King (1940) found a very high incidence of this condition (96·2%) among 13-15-year-old children living in rural crofting communities in the Isle of Lewis, Scotland. In the West Indies he found the incidence less, 83-89% (King and Martin, 1951), though here he was employing a more refined classification.

The association between the occurrence and extent of visible tartar deposits and gingivitis is given for both the Newfoundland age groups in Table 5. In the deciduous teeth tartar was nearly always confined to the upper first and second molars. In the permanent dentition the lower incisor region was also frequently involved. Each child was placed in one of four tartar groups, 0, 1, 2 or 3, according to the area covered on the buccal surface of the upper molars (deciduous and permanent) or the area on the lingual surface of the lower incisor region. It was found that the incidence and extent of gingivitis increased considerably between the children graded tartar-free and those with grade 3 tartar.

Table 7 gives the incidence of cheilosis, blepharitis, tongue changes and roughened skin on the face in the two age groups of 5 and 14 years from the different localities. From this it will be seen that cheilosis and tongue changes were much more frequently observed in the outports of the Burin Peninsula and the Fortune Bay area than elsewhere. Rough skin on the face also tended to be higher in these places, but it was not uncommon even in the inland towns. It was found by Aykroyd *et al.* (1949) and Goldsmith *et al.* (1950) that most of the characteristic signs of malnutrition were less conspicuous and less prevalent in 1948 than in 1944. This they attributed to the several successive attempts on the part of the Government to improve the nutritional situation. The first of these was the enriching of all flour with thiamine, riboflavine, niacine and iron after July, 1944. Since September, 1945, the margarine sold has all been fortified with vitamin A to a level of 45 I.U. per gram, while in November, 1947, the flour was additionally fortified with 0·5% bone meal. Apart from these general measures the special free provision of a hot cocoa-milk powder drink for school children was begun in 1947. Cod liver oil was also made available to schools during the winter months, and concentrated orange juice was provided for expectant mothers and young infants. A propaganda campaign was started to encourage mothers to take up these special foods for themselves and their children, and this has been combined with efforts to improve the local methods of cooking and to encourage the growing of more vegetables.

Diet in Newfoundland

Reference has already been made at the beginning of this paper to the restricted diet available to the average Newfoundlander, especially those living in small settlements. Cuthbertson (1947) gave a detailed report of the situation as he found it two years before this survey was made, and I was able to confirm many of his findings from personal observation. He stated that in the outports the basic diet consisted of fish, white flour (70% extraction), molasses or sugar, margarine and tea, to which were added home-grown cabbages, turnips and potatoes. A little tinned milk, and other imported luxuries were also consumed, but the amount of these depended on the success or failure of the fishing season. Fresh meat was often difficult to obtain, so that fish, frequently salted or dried (almost exclusively the white flesh of cod), and salt pork were the chief sources of animal protein. Wild fruits were stored for winter use, and with potatoes provided the only source of vitamin C for seven or eight months of each year. Families with some livestock did better, but even in their case, climatic conditions and indifferent animal husbandry left them without milk or eggs for many months of the year. The net result was a diet which might have been adequate in calories, but which was very low in all protective foods and calcium. The total carbohydrate intake was above that of neighbouring countries, being 67% as compared with 51% in the U.S.A. and Canada. The phosphorus was high, due to the preponderance of fish and white flour, which probably aggravated the calcium shortage. The intake of the vitamin B complex was also low until the enrichment of the flour in 1945, especially in view of the high carbohydrate consumption. Before the margarine was reinforced with vitamin A it is probable that the intake of this essential food factor was well below the minimum. Eye changes due to its lack were reported as being previously fairly common (Adamson *et al.*, 1945). On such a diet it might be expected that the vulnerable section of the population, the young children and pregnant women, would fare worst.

The work of May Mellanby has shown that the macroscopic and microscopic structure of teeth in several species of animals can be profoundly altered by dietary means during the period of development (Mellanby, 1918, 1920, 1923*b*, 1928). In children's teeth she has shown that very many deciduous teeth do have minor defects (1923*a*, 1927, 1929) which have been termed degrees of M-hypoplasia by King (1940). Such defects are similar to those found in animals reared on experimental diets and are therefore thought to be due to deficiencies in our 'civilized' types of food. May Mellanby and her colleagues have also shown in numerous surveys that children's deciduous teeth with M-hypoplasia are more liable to decay than those of smooth surface texture. On the basis of her animal experiments, the type of diet likely to produce smooth-surfaced teeth in children would be one in which liberal amounts of milk and fat-soluble vitamins were included. She has also shown that teeth may be influenced by this type of diet after eruption in such a way as to arrest decay already present and postpone the development of new caries (Mellanby, 1928; Mellanby and Pattison, 1926; Mellanby, Pattison and Proud, 1924).

If more milk, eggs, fruit, fresh vegetables and regular cod liver oil were to be included in the diets of Newfoundland mothers and of children, especially those under 5 years, this might be expected to reduce the amount of M-hypoplasia and of caries in Newfoundland children.

The Government is trying to encourage the consumption of milk among school children by popularizing the drink of 'cocoa milk' which would give each child the calcium equivalent of one-third of a pint of milk on school days. Cod liver oil is distributed to school children and both it and orange juice are available to children under 5, but the uptake could be much increased. The extra calcium in the bread should help to rectify the low level of this mineral in the average diet.

The Island has done very much better economically since the last war, and in many places there is now well-paid work available as an alternative to fishing; family allowances introduced since the union with Canada should also do much to alleviate the poverty among the many large families. The improvement in the economic situation, however, must be backed up by extensive dietary propaganda if it is to succeed in giving children the type of food they need. All too often higher wages only mean more sweets and soft drinks for the children, instead of more milk and protective foods.

Summary

The results of this survey are based on the examination of 1,486 children, the majority of whom were aged 5 (804) or 14 years (595).

Dental caries was widespread in all localities with the exception of one small area of endemic fluorosis, only 7·2% of the 5-year-old children and under 1% of the 14-year-group being free from caries. The total percentage of deciduous teeth decayed was 38·5, while among the permanent teeth of the 14-year-group, 30·7% were already carious. This corresponds to a decayed-missing-filled

rate per child of 7·4 for deciduous teeth, and of 8·39 for the permanent ones.

Both the deciduous and permanent teeth were found to be of relatively poor structure, only 27·0% of the former and 8·7% of the latter having no M-type hypoplasia.

The percentage incidence of gingivitis, cheilosis, angular fissures, tongue changes and blepharitis were recorded.

The dietetic factors which may have been responsible, at least in part, for this state of affairs, are discussed.

In conclusion I wish to express my thanks to all those who assisted me with the preparatory work of the survey, and in particular to Lady (May) Mellanby for her generous help and encouragement. I am indebted to the Honourable W. H. Quinton, Commissioner of Public Health and Welfare, Newfoundland, for extending to me the facilities of his department. The success of the survey depended to a large extent on the careful plans laid by the Deputy Minister of Health, Dr. Leonard A. Miller, and the Assistant Deputy Minister of Health, Dr. James McGrath, in co-operation with the Department of Education. I was most fortunate to have Miss Ella Brett, B.Sc., Nutritional Adviser to the Department of Public Health and Welfare, Newfoundland, and Nurse Margaret Hall as my personal assistants while carrying out the examinations of the children. The expense of the investigation was met by the Medical Research Council of Great Britain and the Newfoundland Government.

Bibliography

Adamson, J. D., Jolliffe, N., Kruse, H. D., Lowry, O. H., Moore, P. E., Platt, B. S., Sebrell, W. H., Tice, J. W., Tisdall, F. F., Wilder, R. M. and Zamecnik, P. C. (1945). *Canad. med. Ass. J.*, **52**, 227.
Appleton, V. B. (1921). *Amer. J. publ. Hlth.*, **11**, 617.
Aykroyd, W. R. (1930). *J. Hyg., Lond.*, **30**, 357.
—— Jolliffe, N., Lowry, O. H., Moore, P. E., Sebrell, W. H., Shank, R. E., Tisdall, F. F., Wilder, R. M. and Zamecnik, P. C. (1949). *Canad. med. Ass. J.*, **60**, 329.
Coumoulos, H. (1949). *Brit. dent. J.*, **86**, 172.
Cuthbertson, D. P. (1947). 'Report on Nutrition in Newfoundland.' Dominions Office No. 4. H.M. Stationery Office, London.
Dean, H. T., Jay, P., Arnold, F. A. and Elvove, E. (1941). *Publ. Hlth. Rep., Wash.*, **56**, 761.
Fulton, J. T. (1951). *Bull. Wld. Hlth. Org.*, **4**, 1.
Goldsmith, G. A., Darby, W. J., Steinkamp, R. C., Beam, A. S. and McDevitt, E. (1950). *J. Nutr.*, **40**, 41.
King, J. D. (1936). *J. Physiol., Lond.*, **88**, 62.
—— (1940). *Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 241.
—— (1944). *Dent. Rec.*, **64**, 102.
—— and Glover, R. E. (1945). *J. Path. Bact.*, **57**, 353.
—— and Martin, W. J. (1951). *Brit. dent. J.*, **90**, 35 and 63.
Klein, H. (1948). *Publ. Hlth. Rep., Wash.*, **63**, 563.
—— and Palmer, C. E. (1937). *Publ. Hlth. Bull., Wash.*, No. 239.
—— —— and Knutson, J. W. (1938). *Publ. Hlth. Rep., Wash.*, 53, 751.
Knutson, J. W., Klein, H. and Palmer, C. E. (1940). *J. Amer. dent. Ass.*, **27**, 579.
Linghorne, W. J., McIntosh, W. G., Tice, J. W., Tisdall, F. F., McCreary, J. F., Drake, T. G. H., Greaves, A. V. and Johnstone, W. M. (1946). *Canad. med. Ass. J.*, **54**, 106.
Little, J. M. (1912). *J. Amer. med. Ass.*, **58**, 2029.
McDevitt, E., Dove, M. A., Dove, R. F. and Wright, I. S. (1942). *Proc. Soc. exp. Biol., N.Y.*, **51**, 289.
—— —— —— —— (1944). *Ann. intern. Med.*, **20**, 1.
Mellanby, H. (1939). *Brit. dent. J.*, **66**, 76.
—— (1941). *J. dent. Res.*, **20**, 489.
—— (1949). *Brit. dent. J.*, **87**, 321.
—— and Mellanby, M. (1950). *Brit. med. J.*, **1**, 1341.
Mellanby, M. (1918). *Lancet*, **2**, 767.
—— (1920). *Dent. Rec.*, **40**, 63.
—— (1923*a*). *Brit. dent. J.*, **44**, 1.
—— (1923*b*). *Ibid.*, **44**, 1031.
—— (1927). *Ibid.*, **48**, 1481.
—— (1928). *Physiol. Rev.*, **8**, 545.
—— (1929). *Edinb. med. J.*, **36**, (*Trans. Edinb. obstet. Soc.*, **88**, 25.)
—— (1930*a*). *Proc. roy. Soc. Med.*, **23**, 1503.
—— (1930*b*). *Spec. Rep. Ser. med. Res. Coun., Lond.* No. 153.
—— (1939). *Dent. Rec.*, **59**, 227.
—— and Coumoulos, H. (1944). *Brit. med. J.*, **1**, 837.
—— —— (1946). *Ibid.*, **2**, 565.
—— and Mellanby, H. (1948). *Ibid.*, **2**, 409.
—— —— (1951). *Ibid.*, **1**, 51.
—— ——. Unpublished work.
—— and Pattison, C. L. (1926). *Brit. dent. J.*, **47**, 1045.
—— —— and Proud, J. W. (1924). *Brit. med. J.*, **2**, 354.
—— and Shah, M. A. Unpublished work.
Metcoff, J., Goldsmith, G. A., McQueeney, A. J., Dove, R. F., McDevitt, E., Dove, M. A. and Stare, F. J. (1945). *J. Lab. clin. Med.*, **30**, 475.
Murray, M. M. and Wilson, D. C. (1948). *Brit. dent. J.*, **84**, 97.
Schour, I. and Masseer, M. (1947). *J. Amer. dent. Ass.*, **35**, 1.
Scobie, K., Burke, B. S. and Stuart, H. C. (1949). *Canad. med. Ass. J.*, **60**, 233.
Sydenstricker, V. P. (1941*a*). *Ann. intern. Med.*, **14**, 1499.
—— (1941*b*). *Ibid.*, **15**, 45.
Toverud, G. (1949). *J. Amer. dent. Ass.*, **39**, 127.
Weaver, R. (1950). *Brit. dent. J.*, **88**, 231.

THE FUNCTION OF THE ADRENAL GLANDS IN THE NEWBORN*

BY

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It is well known that the adrenal cortex of the newborn infant differs anatomically from that of the adult and that morphological changes take place in the gland during the first few days and weeks of extra-uterine life. Until recent times, however, very little had been known about the function of the adrenal cortex during this period and it is questioned whether or not the adrenal, like the kidney, behaves differently from the adult gland at this time. Efforts have been made to study the problem by assaying the excretion of adrenal cortical metabolites in the urine of newly-born infants and it has been shown that small quantities of such substances not only occur in the first few days of life (Venning, Randall and Gyorgy, 1949; Matson and Longwell, 1949) but also increase significantly in the second week (Read, Venning and Ripstein, 1950). Furthermore the reaction to stress as shown by the response to the administration of epinephrine suggests that the pituitary-adrenal axis is capable of normal function as early as the first day in full-term infants, although premature do not show this response before the ninth day of life (Jailer, Wong and Engle, 1951). It was therefore considered worth while to study further this problem of adreno-cortical function in the newborn and, as a test of adreno-cortical stimulation, the eosinophil count in the peripheral blood and its response to A.C.T.H. was investigated.

Using Thorn's (1948) test a fall in eosinophils of 50% or more below the pre-injection level indicates a satisfactory adreno-cortical response and in all probability eliminates the possibility of adreno-cortical insufficiency. Although 25 mg. A.C.T.H. was described as a suitable test dose for adults, 5 mg. was arbitrarily chosen as an adequate stimulus for newborn infants. The eosinophil counts were made on capillary blood obtained by heel prick by the method of Randolph (1949) using the phloxine propylene glycol stain. An attempt was made to carry out the second part of the test by estimating the uric acid/creatinine ratio in the urine before and after the injection of A.C.T.H.; although a satisfactory method of collecting urine was established, it was found to be impossible to obtain specimens at the appropriate time intervals, as urine excretion may not take place at all during the first 24 hours of life.

Twenty-four normal full-term and 11 premature newborn babies were tested in the manner described as soon after birth as possible during the first 24 hours of life, the majority being tested within the first 12 hours. If the test failed to show a 50% fall in circulating eosinophils, thereby suggesting adreno-cortical insufficiency, it was repeated each 24 hours later until this result was obtained. For control purposes, two eosinophil counts, the second four hours after the first, without the intervening administration of A.C.T.H., were made on 12 normal full term, and six premature, newborn babies during the first and second 24 hours of life.

Results

Full-term Newborn. Of 24 babies, eight did not give a positive test on the first day of life (Table 1).

TABLE 1
RESULTS IN 24 FULL-TERM NEWBORNS

Day of response	1st	2nd	3rd	7th
Number responding	16	6	1	1

With two exceptions (Cases 7 and 13), whose birth weights were over 7 lb., all the infants not responding to the test in the first 24 hours weighed less than 6½ lb. at birth (Table 2).

TABLE 2
BIRTH DETAILS OF EIGHT FULL-TERM NEWBORNS RESPONDING AFTER THE FIRST DAY

Birth Weight (lb. oz.)	Mode of Delivery	Day of Response
7 6	Normal vertex	Second
5 9	Normal vertex	Second
7 11	Normal vertex	Second
6 8	Caesarean section	Second
5 12	Normal vertex	Third
6 0	Normal vertex (diabetic mother)	Seventh
6 0	Caesarean section	Second
6 4	Normal vertex	Second

* Paper read at the first English A.C.T.H. Conference at Harrogate on September 13 and 14, 1951.

Of the eight not responding on the first day, six gave a positive response on the second day.

On the two babies not responding within 48 hours, one, whose birth weight was 5 lb. 12 oz., the smallest in the series, responded satisfactorily on the third day. The other, whose birth weight was 6 lb., did not respond until the seventh day. This infant, the only one in the series taking so long to give a positive test, was the infant of a diabetic mother (Table 3) and was tested on the

TABLE 3
RESULTS IN INFANT OF A DIABETIC MOTHER

Time (Hours after birth)	Eosinophils (per c.mm.)	Blood Sugar (mg.%)
1	Under 5	51
4	180	49
19	Under 5	35
23	30	36

first, second, third, fifth and seventh days of life before a positive response occurred. In fact, on the first four occasions, the eosinophils were less than 5 per c.mm. on initial testing and on three of these four occasions, the administration of 5 mg. A.C.T.H. caused an increase in the number of circulating eosinophils four hours later.

Only two other infants showed a low initial count and a slight rise in eosinophils after the injection of A.C.T.H., one being the 5 lb. 12 oz. infant mentioned previously and the other a 6 lb. 4 oz. infant who responded on the second day.

TABLE 4
DAY OF RESPONSE IN RELATION TO MODE OF BIRTH

Mode of Birth	Birth Weight (lb.	oz.)	Day of Response
Mid forceps	8	3	First
Caesarean section	7	13	First
Caesarean section	6	8	Second
Forceps	7	1	First

The mode of birth did not seem to have any effect on the subsequent response to the A.C.T.H. test (Table 4). Two infants born by forceps extraction and one born by Caesarean section responded on the first day, but one other Caesarean baby, whose weight was 6 lb. 8 oz., did not respond till the second day.

Apart from the infant of the diabetic mother, the initial eosinophil counts ranged from 40 to 1,030 per c.mm., while those of the controls varied from 40 to 820 per c.mm.

Premature Newborns. Of the 12 babies tested (Table 5), four did not give a positive reaction on the first day but responded when tested on the

TABLE 5
RESULTS IN 12 PREMATURE NEWBORNS

Day of response	1st	2nd
Number responding	8	4

second day of life. These four babies showing the delayed response were the smallest babies in the series (Fig. 1). Apart from one premature

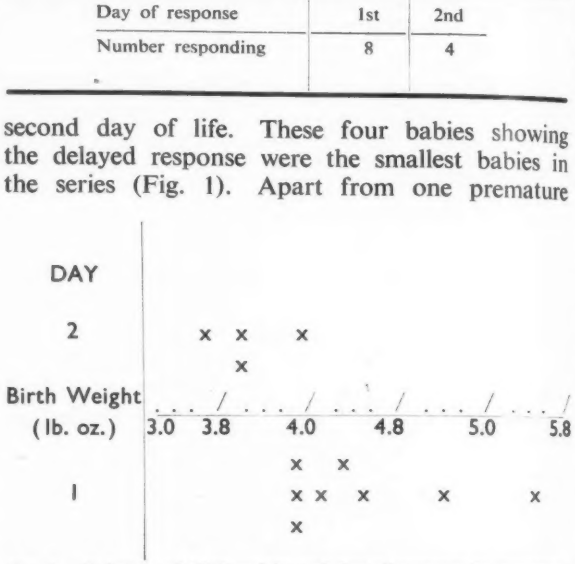

FIG. 1.—Relation of birth weight and day of response in premature newborns.

infant with an eosinophil count of 1,400 per c.mm., the range of eosinophils varied from 10 to 260 per c.mm., and, as in the case of the controls, the values recorded were much lower than those of the normal full-term babies.

Controls. Twelve full-term and six premature newborn babies were not given A.C.T.H. but the eosinophils were counted on two occasions four hours apart on the first day of life. Only two of the 18 babies investigated showed a 50% decrease in eosinophils when the two counts were compared. Usually the second count equalled or was slightly higher or lower than the first. On no occasion on the second day of life was a 50% decrease in eosinophils recorded when the two counts were compared.

Discussion

As a result of this investigation, it would appear that adreno-cortical function as measured by the eosinophil response to A.C.T.H. is normal in the majority of newborn infants on the first day of life. Some infants, in the present series one-third, failed to show normal function during the first 24 hours, but most of these gave a normal response on the second day. The smallest baby in the series, whose birth weight was 5 lb. 12 oz., did not respond till the third day.

Similarly the majority of premature newborns showed normal adreno-cortical function by this

test during the first 24 hours of life but the smallest babies in this group, all with birth weights of 4 lb. and under, did not give a normal response till the second day of life.

Newborn infants are less sensitive to A.C.T.H. than older ones (Venning *et al.*, 1950) and the small dose, 5 mg. of A.C.T.H., used may be the reason for the failure of response on the first day by some of the newborns.

Using the same test of adreno-cortical function in infants during the first and second weeks of life, Klein and Hanson (1950) reported much less response in infants in the first week than there was in infants over one week of age. The observations reported here suggest that adreno-cortical function is normal in the majority of full-term and premature newborns on the first day of life, and the remainder, most of whom are the smaller and more immature, show normal function by the second or third day. These results confirm those of Jailer, Wong and Engle (1951) in America and Bergstrand, Hellström and Jonsson (1951) in Sweden, who found that A.C.T.H. produced eosinopenia in both full-term and premature infants as early as the second or third day of life.

Thus it would appear that although the adrenal cortex is histologically different from that of the adult, it responds in the same way physiologically.

The exception to the foregoing was the infant born of a diabetic mother. This infant continued to show low eosinophil counts during the first week of life and did not develop normal adreno-cortical function till the end of the first week. One might speculate that the hypoglycaemia found in this infant after birth and the failure to develop normal adreno-cortical function were interconnected and due to the lack of adreno-cortical hormones. The low eosinophil counts recorded before A.C.T.H. was given might be the response to maternal adrenal steroids, pre-supposing that these cross the placental barrier in a manner similar to gonado-tropins and oestrogen, and further work on this type of infant and this aspect of the problem is contemplated.

Summary

A.C.T.H., 5 mg., was given to 24 full-term and 12 premature newborn infants, and the changes in circulating eosinophils were measured.

Sixteen of the full-term and four of the premature babies showed a normal response as shown by a 50% decrease in eosinophils on the first day of life.

All but two of the remainder showed a normal response on the second day of life.

One baby, whose birth weight was 5 lb. 12 oz., responded on the third day, but an infant born of a diabetic mother did not give a normal response till the end of the first week.

It is concluded that although the adrenal cortex is anatomically immature in the first days of life, its function is normal in the majority of newborn and premature babies on the first day and in the remainder on the second day of life.

My thanks are due to Professor Wilfrid Gaisford and Dr. Sylvia K. Guthrie for permission to carry out this investigation in the nurseries at St. Mary's Maternity Hospital, Manchester, and the Premature Unit at the Duchess of York Hospital for Babies, Manchester. The A.C.T.H. was kindly supplied by the Armour Laboratories, Chicago.

REFERENCES

Bergstrand, C. G., Hellström, B. and Jonsson, B. (1951). *Acta paediat., Uppsala*, **40**, 369.
Jailer, J. W., Wong, A. S. H. and Engle, E. T. (1951). *J. clin. Endocr.*, **11**, 186.
Klein, R. and Hanson, J. (1950). *Pediatrics*, **6**, 192.
Matson, C. F. and Longwell, B. B. (1949). *J. clin. Endocr.*, **9**, 646.
Randolph, T. G. (1949). *J. Lab. clin. Med.*, **34**, 1696.
Read, C. H., Venning, E. H. and Ripstein, M. P. (1950). *J. clin. Endocr.*, **10**, 845.
Thorn, G. W., Forsham, P. H., Prunty, F. T. G. and Hills, A. G. (1948). *J. Amer. med. Ass.*, **137**, 1005.
Venning, E. H., Randall, J. P. and Gyorgy, P. (1949). *Endocrinology*, **45**, 430.

BILATERAL PHAEOCHROMOCYTOMA IN A 6-YEAR-OLD BOY

BY

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Chromaffin cell tumours are rare in children. We have been able to find only nine cases recorded in the literature under the age of 13 years, the youngest being an infant of 18 months. Snyder and Vick (1947) review the four cases previously reported and add a further three of their own. Goldenberg, Snyder and Aranow (1947) also discuss two of these children and include an eighth case. In eight cases operative removal was attempted, and was followed in four children by complete clinical recovery. One of these successes, described by Grimson, Longino, Kernodle and O'Rear (1949), was attributed, in part to the use of adrenolytic drugs. Of the remainder, three died from post-operative collapse and one from congestive cardiac failure six weeks later; a second tumour was found at necropsy in the latter case (Linneweh, 1942). More than one tumour was present in three of these nine cases.

We are presenting this case, which was fatal, partly on account of its rarity and partly to draw attention to the problems of differentiation from pink disease (or juvenile acrodynia), problems which are, we feel, of significance not only in this case, but also in relation to the possible aetiology of pink disease.

Case Report

P.S., a boy aged 6 years, was admitted on August 11, 1948, under the care of Dr. N. M. Jacoby. For six weeks before admission he had suffered from persistent lethargy and night sweats. A single attack of vomiting occurred at the onset of his illness. His previous health had been good except for measles and whooping cough. His mother, father and sister, aged 3½ years, were all healthy.

On admission he was a thin, anxious-looking child with a sallow complexion, and weighed 38 lb. His worried expression was emphasized by widened palpebral fissures and slight exophthalmos (Fig. 1). Both hands were cold and sweating, bluish-pink, and with a very marked capillary pattern; the skin and subcutaneous tissues were thickened and showed a firm, non-pitting oedema. These changes extended about 1½ in. above the wrists. When warm, the hands became dusky pink and their appearance was indistinguishable from that seen in acrodynia. At the time of admission the mother stated that these changes had been present since infancy, but later said that they had become more marked recently. The feet were possibly slightly pinker than normal but the changes were never convincing. The child sometimes rubbed his hands and feet, but there were no parasthesiae and despite their abnormal appearance he never complained of pain or irritation in the extremities.

There was a tachycardia of 120. Marked arterial pulsation was present in the neck; all the peripheral pulses were slapping in character. The blood pressure in the arms was 190/130 mm. Hg. A later reading of 150/130 mm. Hg in the arms was obtained, the systolic pressure in the legs being 145 mm. on that occasion. The heart was not clinically enlarged; the heart sounds were loud and forceful, and no murmurs were heard.

The abdomen was full. The liver edge was palpable two fingerbreadths below the costal margin. No other masses were felt.

There was marked hypotonia, but all reflexes were preserved throughout the course of the disease and there were no sensory changes. The ocular fundi showed arterial narrowing, but no haemorrhages or exudates were present.

Laboratory Investigations. A blood count gave: Hb. 84%; R.B.C. 5,230,000; W.B.C. 20,000 (polymorphs 55%, stabs 5%, lymphocytes 40%). The basal sedimentation rate was 40 mm. in an hour (Westergren).

The tuberculin jelly test was negative, as also was the Wassermann reaction.

Repeated examinations of the urine showed a moderate degree of albuminuria but no other abnormality. The blood urea was 22 mg./100 ml., the urea clearance normal. An Addis count on a 12-hour specimen gave: total volume 460 ml., R.B.C. 184,000; no pus cells or casts; serum sodium level 297 mg./100 ml.; serum potassium level 25·3

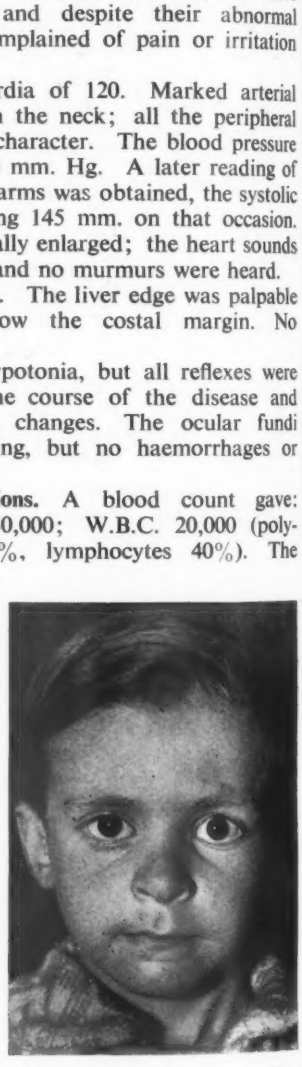

FIG. 1.—P.S., aged 6 years. The typical anxious expression with some exophthalmos is shown. The pupils are dilated with atropine.

mg./100 ml. and serum chlorides 630 mg./100 ml.; serum cholesterol level 213 mg./100 ml. Repeated serum potassium estimations gave 22·7 mg./100 ml.

A radiograph of the chest showed a heart that was slightly enlarged with a suggestion of left ventricular hypertrophy. A radiograph of the long bones was normal. The skull showed no abnormality in the region of the pituitary fossa (Dr. C. H. Hodson).

An E.C.G. showed that the standard limb leads and one chest lead were normal.

While in hospital the patient retained his apprehensive expression, although he was quite cooperative and apparently fairly happy in his relations with other children and the ward staff.

He was subject to frequent attacks of profuse sweating, usually during the night. No precipitating factors were discovered, but the child was sometimes aware that an attack was imminent. He became very pale and quiet and complained of severe headache and occasionally of nausea. This was followed after an interval of 20 to 30 minutes by profuse, drenching perspiration. During attacks his blood pressure, which varied from 150/130 to 180/150, was raised to 240/156. A tachycardia of 120-140 was present at all times; there appeared to be an inconstant increase in rate during attacks, when the pulse became thready and difficult to feel. During a paroxysm multiple extrasystoles were present: it is probable that the recorded radial pulse rate was deficient.

While under observation he was very constipated. He was afebrile but continued to show a slight leucocytosis and a raised sedimentation rate of 30-40 mm. in one hour. The pinkness of the hands became more pronounced, and he developed a generalized sudaminous rash associated with marked desquamation of the hands and slight desquamation of the feet. He was seen at this time by many paediatricians who considered that he showed the classical features of pink disease.

The differential diagnosis at this stage was considered to lie between pink disease, a phaeochromocytoma and periarteritis nodosa. The sweating, rash, tachycardia, persistent hypertension and increased nervous tension, in association with the marked erythromelalgia of the hands, suggested pink disease, whereas the paroxysmal hypertensive attacks favoured a phaeochromocytoma.

Diagnostic Tests. In an attempt to confirm or disprove the presence of a phaeochromocytoma, the following further investigations were performed. Repeated attempts to induce hypertensive paroxysms by pressure in the renal angles failed. Estimation of B.M.R. (Dr. Clarke, Royal Free Hospital) gave +145%, an unsatisfactory test as the child was sweating profusely throughout. Sodium amytal, grain ¾, for three doses was given, but blood pressure was not depressed and during the third hour he developed a typical paroxysm.

The benzodioxane test (933F Fourneau) with piperidylmethyl benzodioxane was applied. The technique described by Goldenberg *et al.* (1947) was adopted. An intravenous saline drip was set up and an attempt made to stabilize the patient's blood pressure. After two hours, however, it was still 200/170, i.e. raised 10-15 mm. above the resting level. Benzodioxane, 7 mg. (933F Fourneau) was injected with an intravenous needle, but as the child screamed at the sight of the syringe the injection was given more rapidly than advocated by Goldenberg in order to minimize a psychological pressor response. A transient fall to 170 mm. systolic (i.e. lower than for four weeks previously) was obtained, but not a sustained fall such as reported by Goldenberg in his cases. This may perhaps be ascribed to the rapidity of the injection and the failure to stabilize the blood pressure at his resting level beforehand, or to excessive secretion by the tumour at this time.

Goldenberg (Goldenberg and Aranow. 1950) comments that 'standard doses of benzodioxane may be inadequate to combat the effects of such large outpourings of amines as may occur in some paroxysms of hypertension'. In retrospect there is no doubt that this test should have been repeated (Fig. 2*a*).

A control injection in an infant with pink disease was carried out. The reaction followed the pattern described by Goldenberg for cases of hypertension of miscellaneous origin. The technique in this case was satisfactory (Fig. 2*b*).

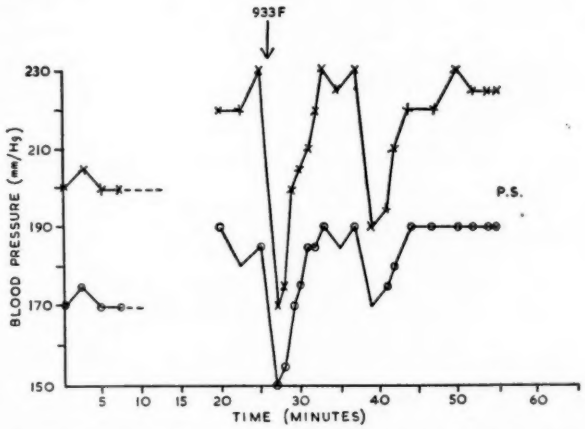

FIG. 2*a*.—Blood pressure recordings after injection of 933F on P.S. A transient fall only is recorded.

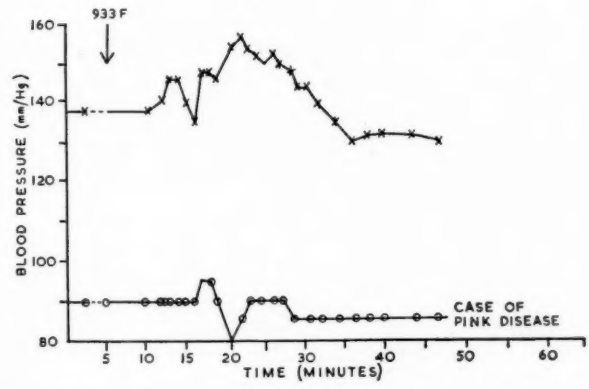

FIG. 2*b*.—Blood pressure recordings after injection of 933F on a case of pink disease with hypertension. A rise in systolic pressure is shown.

A radiograph of the abdomen and an intravenous pyelogram (Dr. C. H. Hodson) were made. Throughout this child's film series there were two small groups of persistent opacities. One lay in the region of the right twelfth rib about 3 in. from the middle line and the other at a rather lower level on the left about 2½ in. from the midline. Beyond saying that they could lie in relationship to the upper renal poles, there was nothing particular about their nature or situation.

When intravenous pyelography was carried out the pelvicalycine patterns were found to be normal and the renal outlines also appeared normal, except perhaps for a slight blunting of the upper pole of the right kidney, which could have been due to the liver. The opacities were now seen to overlie both upper poles of the kidney being slightly lower on the left side than on the right. This indefinite type of shadowing is commonly found in phaeochromocytoma.

Perirenal insufflation was carried out by Mr. Swain; 260 ml. air were injected into the right perirenal space. A temporary respiratory arrest occurred, and although recovery was satisfactory, no attempt was made to insufflate the left side. The lower pole of the right kidney only was outlined.

The histamine test meal was omitted owing to the risk involved, as the naturally occurring paroxysms were very severe.

Reviewing the case at this stage it was decided that evidence in favour of the diagnosis of a phaeochromocytoma was suggestive, but not strong enough to warrant exploratory laparotomy.

After four months the clinical condition was unchanged, except for the development of left ventricular hypertrophy and a loss of 2 lb. in weight. The sweating attacks were apparently less frequent, but the hypertension persisted in the range of 185-205/140.

The parents were against the performance of an exploratory laparotomy and, as no other active treatment was advised, removed him from hospital.

After three months at home, he showed little change in his condition. The hypertension persisted. The parents eventually agreed to further investigation and he was readmitted on April 27, 1949, approximately 10 months after the original onset of symptoms. He then weighed (26 lb.) and his blood pressure was 185/120 mm. Hg. No masses could be felt in the renal angles although the extreme constipation made abdominal palpation difficult.

A minute volume test to assess renal function was planned. The patient was anaesthetized satisfactorily but collapsed when urethral dilators were passed and failed to respond to resuscitation.

Necropsy. Dr. C. K. Simpson performed the necropsy. Some chronic oedema of the hands was present but there was no 'acrocyanosis' and no subungual or other petechiae.

ADRENAL GLANDS. The position of the left adrenal gland was occupied by a well-circumscribed, smooth, ovoid, yellowish-brown tumour which measured 6 × 5 × 4 cm. (Fig. 3). Projecting from its upper pole were five small nodules, the largest of which was 2·0 cm. in diameter. The tumour extended downwards over the antero-medial aspect of the kidney which, although distorted by the presence of the mass, showed no evidence of infiltration. On the cut surface the centre was brown and homogeneous whilst the more superficial part was of a softer consistency and more yellowish. A thin layer of connective tissue covered the tumour, separating it from the retroperitoneal tissue. Attached to its upper and lateral aspect were the remains of the adrenal gland, represented by a triangular piece of apparently normal adrenal cortex measuring 3·0 × 2·5 × 1·5 cm., giving the impression that the tumour had arisen in the medulla and ultimately broken through the cortex.

The right adrenal gland showed a tumour measuring 3·0 × 2·5 × 1·5 cm. occupying the position of the medulla and extending medially and downwards towards the hilum of the kidney. Its cut surface had a similar appearance to that of the left tumour, although there was distinct lobulation. The adrenal cortex was present in normal amount and was stretched over the greater part of the tumour. Unfortunately no biochemical assays of the tumour were made.

HEART. The heart weighed 298 g. (normal 100 g.). The left ventricle showed concentric hypertrophy and a moderate degree of dilatation. Its wall was 1·2-2·0 cm. thick. The right ventricle was slightly dilated and its wall was 0·3-0·6 cm. thick. Several small yellow patches were present on the anterior cusp of the mitral valve and definite atheroma surrounded the orifices of the right coronary artery and all the posterior intercostal arteries. The coronary arteries were normal.

The liver (1,106 g.) was pale with distinct fatty change at the periphery of the lobules. The hilar and mediastinal lymph nodes were moderately enlarged. All other organs were normal.

FIG. 3.—The left adrenal gland showing replacement by phaeochromocytoma.

The cause of death was vagal inhibition during the passage of urethral dilators.

MICROSCOPY. Dr. N. France examined tissue from the tumours fixed in Zenker-formalin solution for 24 hours followed by immersion in 2·5% potassium dichromate for seven days. Beneath a well-defined fibrous capsule occasional cells resembling those of adrenal cortex were present and these merged with the tumour itself. The tumour consisted of cells varying in size and shape, frequently with ill-defined margins. They were arranged in groups separated by loose connective tissue containing small capillaries (Fig. 4). The cells possessed round or oval, vesicular nuclei with prominent nucleoli and faintly eosinophilic cytoplasm. They were occasionally multinucleated and sometimes vacuolated (Fig. 5). Some cells contained chromaffin granules but the majority showed no reaction. Mitotic figures were scanty. The centre of the tumour was occupied by collagenous fibrous tissue in which were scattered isolated cells showing marked chromaffin staining. Despite the variation in the cells and the presence of occasional giant cells, the tumour was considered to be benign.

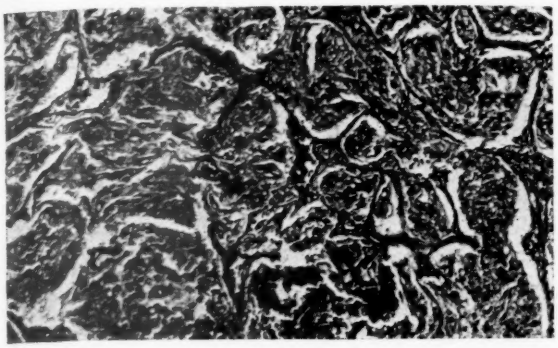

FIG. 4.—Section of tumour (×59) showing general arrangement of cells in groups.

The muscular coats of many of the smaller arteries in the kidney were hypertrophied, and some showed fibrinoid degeneration of the intima in the absence of duplication of the internal elastic lamina. There was no evidence of glomerular damage, malignant hypertension or scar formation. Arterial changes were even more marked in the spleen where fibrinoid degeneration was a prominent feature. The aorta showed great thickening of the intima with fatty change characteristic of established atheroma. There was considerable fatty change of the liver affecting the greater part of the lobule with moderate congestion of the central zone. All other organs of the brain were normal. No histological examination of the central nervous system was made.

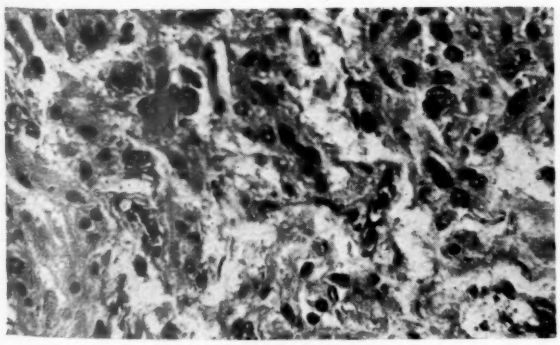

FIG. 5.—Section of the tumour. ×230.

Discussion

Our patient closely resembled in facial appearance and in his simulation of acrodynia the case reported by Snyder and Vick (1947) of a phaeochromocytoma in an 11-year-old boy. Vascular disturbances affecting the extremities have been noted by several authors in adults with phaeochromocytoma. Pallor and mottled cyanosis during attacks followed by flushing during the recovery phase has been described by Calkins and Howard (1947), by Ferraro and Angle (1948) and by Spalding (1947). The hands of these patients were apparently normal between the hypertensive crises, and all were subject to typical paroxysms of hypertension. Smithwick, Greer, Robertson and Wilkins (1950) stress the importance of peripheral vascular phenomena, which were present in nine out of 10 of their cases, in the differential diagnosis of phaeochromocytoma and essential hypertension. McCullagh and Engel (1942) describe a 19-year-old girl who had a persistent, glove-like distribution of erythema. It is probable that the recurrent severe anoxaemia caused by the intense arteriolar constriction caused temporary exudation of plasma into the subcutaneous tissues, producing chronic oedema in our case. Peripheral vascular changes, sometimes of a severity comparable with those seen in acrodynia, are therefore not uncommon in cases of biologically active phaeochromocytoma. The variation in the degree of peripheral vascular changes seen is possibly due to the fact that phaeochromocytoma may secrete predominately adrenaline or *nor*-adrenaline, or both, the latter having a more powerful and generalized peripheral vaso-constrictor action (von Euler, 1951).

The only other case we have found presenting a similar clinical picture was that of Anderson (1944) of acrodynia in a 9-year-old boy; this child had gross hypertension, with paroxysmal exacerbations associated with sweating. He was about to have a laparotomy performed when he suddenly developed pinkness of the extremities and a diagnosis of acrodynia was made. He recovered completely 16 months from the onset of symptoms.

Differential Diagnosis from Acrodynia. The skin changes, sweating, tachycardia and hypertension were all similar to those found in acrodynia.

Paroxysmal hypertension has not been recorded in this disease (except in Anderson's case quoted above), but this may be because the blood pressure has not been taken during sweating attacks. On studying the literature one is impressed by the very occasional blood pressure recordings actually given, possibly because the technical difficulties involved are considerable. It should be noted, however, that the absence of paroxysmal hypertension does not exclude a diagnosis of phaeochromocytoma. This point is stressed by Green (1946) in his review of the subject. Of the nine cases in the paediatric age group only four had typical attacks of paroxysmal hypertension while under observation, the remainder having sustained hypertension.

Also our child's personality did not show the typical changes of acrodynia: profound misery and irritability in infancy, and almost psychiatric changes in older children and adults. The other atypical feature was the child's age: the age limits are almost invariably between 6 months and 4 years. Wyllie and Stern (1931) mention but do not describe a case with symptoms starting at 3 weeks of age. Cases in children over 4 years are mentioned but no clinical details given by Warkany and Hubbard (1948), Blackfan and McKhann (1933) and Zahorsky (1922). A syndrome resembling pink disease has been described in adults by White (1926), and otherwise exclusively in the French literature of the Lyons school. White's cases are extremely doubtful, and the localization of all the reported cases to one area makes it probable that there is some local factor involved producing this particular clinical picture. References to some of these cases are quoted by Griffiths (1950). Similarly, an acrodynia-like syndrome can be produced experimentally in rats by a diet deficient in essential fatty acids (Kummerow, Chu and Randolph, 1948) and in man by chronic arsenical poisoning (Petren, 1921). But we have been able to find only two cases starting later than 4 years of age which appear to be clinically identical with infantile acrodynia (Anderson, 1944; Mouriquand, Dechaume, Bernheim and Weill, 1935), and therefore now feel that such a diagnosis should be made with the greatest caution, if at all.

The literature on acrodynia is marked by a paucity of clinical facts and a plethora of theories. In view of the striking simulation of acrodynia by our case we should like to draw attention to the theory, originally postulated by Kühl (1927), that the disease is due to hyperfunction of the adrenal medulla associated with hypofunction of the adrenal cortex, and that the sharply demarcated age limits are due to its being an exaggeration of the normal physiological post-natal changes in the cortico-medullary interrelationships.

Many of the other aetiological theories are discussed by Cheek (1950), who stresses the importance of adrenocortical insufficiency in acrodynia, and by Leys (1950), who describes the disease as a diencephalopathy. We can only suggest that it may be of interest in future cases of acrodynia to look for evidence of adrenal medullary hyperactivity first by seeing if the characteristic sweating attacks are associated with hypertensive paroxysms (the use of a sphygmo-oscillometer should make this simpler than it has been in the past), and secondly perhaps by physiological experiments using the patient's serum, as suggested by Kühl (1927), or by urinary assay (von Euler, 1950), and thirdly by the use of the benzodioxane test.

Summary

A case is reported of a bilateral phaeochromocytoma in a 6-year-old boy who showed peripheral vascular changes and hypertension.

The differential diagnosis from acrodynia is discussed.

Early laparotomy in any similar future case is recommended in view of the diagnostic difficulties.

We wish to thank Dr. N. M. Jacoby for permission to publish the case: Dr. C. K. Simpson and Dr. Heady for permission to quote the post-mortem findings and Dr. N. France for the histological studies.

References

Anderson, K. (1944). *J. Pediat.*, **24**, 186.
Blackfan, K. D. and McKhann, C. F. (1933). *Ibid.*, **3**, 45.
Calkins, E. and Howard, J. E. (1947). *J. clin. Endocr.*, **7**, 475.
Cheek, D. B. (1950). *Med. J. Aust.*, **1**, 101.
Euler, U. S. von (1951). *Brit. med. J.*, **1**, 105.
Ferraro, L. R. and Angle, R. G. (1948). *Arch. intern. Med.*, **81**, 793.
Goldenberg, M. and Aranow, H. (1950). *J. Amer. med. Ass.*, **143**, 1139.
——, Snyder, C. H. and Aranow, H. (1947). *Ibid.*, **135**, 971.
Green, D. M. (1946). *Ibid.*, **131**, 1260.
Griffith, G. (1950). *Edinb. med. J.*, **57**, 162.
Grimson, K. S., Longino, F. H., Kernodle, C. E. and O'Rear, H. B. (1949). *J. Amer. med. Ass.*, **140**, 1273.
Kühl, G. (1928). *Z. Kinderheilk.*, **45**, 315.
Kummerow, F. A., Chu, T. K. and Randolph, P. (1948). *J. Nutr.*, **36**, 523.
Leys, D. (1950). *Archives of Disease in Childhood*, **25**, 302.
Linneweh, F. (1942). *Mschr. Kinderheilk.*, **90**, 179.
McCullagh, E. P., and Engel, W. J. (1942). *Ann. Surg.*, **116**, 61.
Mouriquand, —., Dechaume, J., Bernheim, —. and Weill, L. (1935). *Lyon méd.*, **156**, 203.
Petren, K. (1921). *Rev. neurol., Paris*, **28**, 812.
Smithwick, R. H., Greer, W. E. R., Robertson, C. W. and Wilkins, R. W. (1950). *New Engl. med. J.*, **242**, 252.
Snyder, C. H. and Vick, E. H. (1947). *Amer. J. Dis. Child.*, 73, 581.
Spalding, J. M. K. (1947). *Brit. med. J.*, **1**, 564.
Swan, H. J. C. (1949). *Lancet*, **2**, 508.
Warkany, J. and Hubbard, D. M. (1948). *Lancet*, **1**, 829.
White, C. J. (1926). *J. Amer. med. Ass.*, **87**, 1092.
Wyllie, W. G. and Stern, R. O. (1931). *Archives of Disease in Childhood*, **6**, 137.
Zahorsky, J. (1922). *J. Mo. med. Ass.*, **19**, 296.

SPONTANEOUS RUPTURE OF THE HEART IN THE NEWBORN INFANT

BY

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The pericardial sac of the newborn infant is frequently found at necropsy to contain a small quantity of thin, serous fluid, usually greenish; in the full-term infant this may amount to as much as 3 or 4 ml. When, in an attempt at resuscitation, an intracardiac injection has been made shortly before death, this pericardial effusion may be tinged with a variable amount of blood, and the site of entry of the needle into the heart is usually clearly visible as a tiny area of subpericardial haemorrhage on the ventricular wall. Such a slight degree of traumatic haemopericardium is seldom of any significance, since the myocardium closes over the needle track and effectively seals it so that no more blood can be expressed from the site of injection. On the other hand, haemopericardium due to spontaneous rupture of the heart is a very rare condition in the newborn, and the following case, in which the lesion occurred shortly before delivery, is presented as an example of an unusual cause of stillbirth.

Case Report

The mother, a primigravida, was aged 28 years; blood group A Rh-positive. Her Wassermann reaction was negative. She had a long history of varicose veins with ulceration of the right leg, and four years before this pregnancy she had been admitted to hospital for a Trendelenberg's operation, and again, in the following year, for ligation and excision of the veins below the knee. Otherwise her past history was uneventful. Both her parents died in old age, her father of cardiovascular disease, and her mother of 'senile degeneration'; she had no brothers or sisters. Her husband was a twin. The pregnancy was normal except that the foetus presented as a breech, and at the thirty-sixth week of pregnancy she was admitted for external cephalic version under sedation. The foetal heart rate both before and after the version, which was unsuccessful, was 140 per minute. Two weeks later the membranes ruptured spontaneously and the patient was admitted in labour, with the cervix fully dilated. The first and second stages of labour lasted three and a quarter hours and resulted in the delivery of a stillborn foetus as an assisted breech under gas, oxygen, and trilene anaesthesia. Twenty-five minutes before delivery there was some doubt whether the foetal heart could be heard, but it was not heard immediately before delivery, nor was there any pulsation in the cord when the foetus had been delivered as far as the umbilicus. No intracardiac injection was given after delivery. The third stage of labour, which lasted three hours, was complicated by a retained placenta, which required manual removal under gas, oxygen, trilene and ether anaesthesia. It was then discovered that the mother had a bicornuate uterus, and the placenta, which was not morbidly adherent, was present in the right horn. One pint of group A Rh-positive blood was given, after which the puerperium was uneventful.

Macroscopic Examination. The body was that of a fresh female foetus of approximately 38 weeks maturity. The weight was 2·58 kg., and the length, crown-rump 34 cm., crown-heel 49 cm. There were no external features of note, and no cyanosis or oedema.

The thoracic contents were exposed by incising the costal cartilages at the lateral ends, and removing the sternum by blunt dissection to avoid injury to the underlying structures. The pericardial sac was found to be greatly distended by a large amount of fresh fluid blood. When this had been removed, and the heart had been gently wiped clean, a slow ooze of blood was seen issuing from a point on the anterior aspect of the right atrium, close to the root of the atrial appendix; examination of this area under 30 magnification revealed a tiny round perforation in the atrial wall, less than 0·5 mm. in diameter. The right atrium was moderately distended; the other chambers, all of which contained fluid blood, appeared normal in size. No subpericardial haemorrhages were found. All the cusps of both the mitral and tricuspid valves showed on the internal surfaces numerous rounded haematomata of varying sizes, the largest being approximately 1 mm. in diameter. The aortic and pulmonary valves and the great vessels were normal, and the ductus arteriosus was patent. The coronary vessels, which followed their normal course, were not engorged, and the myocardium showed no unusual features apart from the perforation in the right atrium.

There was no fluid in the pleural sacs. The trachea was clear, but both bronchi were completely occluded by a mass of thick mucus. The lungs were uniformly plum-coloured, with a few subpleural petechiae, and they showed no evidence of aeration; both lungs, and all portions from them, sank in water.

The stomach, intestines, liver (135 g.), spleen (8 g.) and pancreas were normal. There was a small spherical

accessory spleen, 5 mm. in diameter, lying in the gastro-splenic ligament. The right kidney lay at a more caudal level than the left, so that it was completely separated from the right suprarenal gland. In both kidneys there was much haemorrhage surrounding the pelvis and calyces, but the cut surface showed a normal renal pattern. Since it did not lie in contact with the kidney, the right suprarenal showed no evidence of moulding on its inferior surface, but had assumed the shape of a flattened, oval disc, with diameters of approximately $2 \times 4 \cdot 5$ cm.: the left suprarenal was normal. The head showed a slight subcutaneous haemorrhage near the anterior fontanelle, but there was no intracranial haemorrhage, and the dural membranes were undamaged. The brain showed considerable congestion, both externally and internally, but was otherwise normal.

Microscopic Examination. Serial sections were cut in the coronal plane through the anterior wall of the right atrium in the region of the perforation. Of these sections, that illustrated in Fig. 1 shows the perforation at its widest part; it appeared as an interruption in the continuity of the atrial wall, measuring approximately 140μ between the torn edges of the visceral pericardium. On each side of the rupture there was a small mass of acellular hyaline material, which gave a strongly acidophilic reaction with haematoxylin and eosin and with carbol fuchsin, and the rupture appeared to have occurred through this area of hyaline degeneration; the myocardium on the immediate right-hand side of the rupture was affected by a similar change, but the degeneration in these fibres was not as far advanced as at the site of the rupture. There was no evidence in this, or in any of the serial sections, of any cellular reaction or fibrosis in the region of the perforation, and the neighbouring capillaries were normal and showed no obstruction or occlusion. The lesion did not resemble an infarct, but rather appeared to be a small zone of hyaline degeneration occurring in the myocardium at a point where the latter was very thin. Although there were several other places in the atrial wall where the myocardium was reduced to a thickness of not more than 2 or 3 cells (one such place is included near the lower left-hand edge of Fig. 1) no other evidence of hyaline change was seen in the atrial wall, the myocardium of which appeared entirely normal.

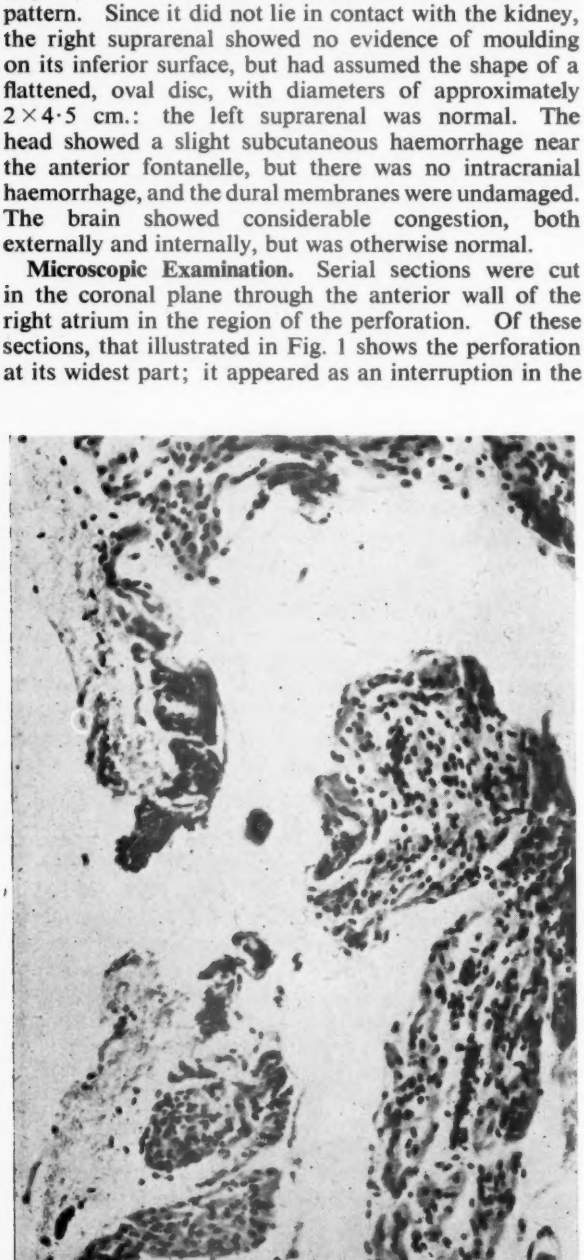

FIG. 1.—Photomicrograph of part of the anterior wall of the right atrium showing the site of rupture, and the hyaline degeneration of the myocardium on each side of the gap in the atrial wall. Haematoxylin and eosin (×150).

The only other feature of note in the heart was seen in a section from the anterior wall of the right ventricle, which included part of the anterior cusp of the tricuspid valve. Within the latter were three large, round, circumscribed haematomata, stuffed with erythrocytes, and showing no evidence of coagulation. Since such collections of blood in the valve cusps are a fairly common finding in the heart of the newborn infant, these lesions were not in any way related to the degeneration of the atrial wall. The ventricular myocardium and the coronary vessels were normal.

Discussion

The great majority of cases of spontaneous rupture of the heart occur in old persons, the incidence being highest in the seventh and eighth decades. Diamond (1945) found that the average age of patients dying with rupture of the ventricle was 66 years, and in their analysis of 602 cases, which included three previously reported series, Krumbhaar and Crowell (1925) found only four occurring in the first decade, but they did not give the ages of these patients. Lyon (1950) states that haemorrhage into the pericardial sac can occur in the neonatal period as a result of birth trauma, and rarely in cases of blood dyscrasia, but he does not mention spontaneous rupture of the heart as a cause of haemopericardium in infancy.

Acute spontaneous haemopericardium in the adult may arise from a number of lesions, of which rupture of a myocardial infarct is the commonest (Fulton, 1940). Myocardial infarction has been found in patients of all ages, and is known to occur in infancy. In a survey of the literature Ravich

and Rosenblatt (1947) were able to collect four reported cases, the ages of which ranged from 7 weeks to 11 months, and they added two further examples in infants dying at 2 days and 10½ hours respectively, thus showing that the lesion could develop during intra-uterine life. Another instance was reported by Knop and Bennett (1944): in this infant, who died at the age of 5 days, the lesion was associated with congenital absence of the left coronary artery and an inadequate left branch from the right coronary.

None of these cases, however, was complicated by rupture of the heart, and the only recorded example of such a lesion in the newborn appears to be that of Benmussa, Caruana and Hamza (1950) in an infant who died at the age of 24 days. The child, a boy, was admitted to hospital on the seventeenth day with diarrhoea and failure to gain weight. He was treated with subcutaneous fluids, penicillin and sulphadiazine, but developed signs of pneumonia and died suddenly during an intense cyanotic attack seven days after admission. At necropsy the mediastinum was found to be full of blood, and there was a laceration of the parietal pericardium extending over the whole of its anterior surface; the haemorrhage had arisen from a horizontal rupture of the right ventricle, 2 cm. in length. The coronary arteries appeared normal on naked-eye examination, and, apart from a patent ductus arteriosus, there were no other lesions in the heart or great vessels. There was also evidence of acute enteritis and bronchopneumonia. Microscopically there was capillary stasis, with some small haemorrhages and phagocytosis of pigment granules, in the region of the rupture, but, for the most part, the myocardial fibres showed no degeneration except at one point. Unfortunately, the coronary arteries were not examined microscopically, and the authors could find no cause for the haemorrhagic infarction that had resulted in the rupture of the right ventricle; they suggest, however, that certain factors may have contributed to the formation of the rupture. Thus, 24 hours before death, the infant was inadvertently given as much as 150 ml. of plasma intravenously in only 15 minutes, and this sudden overloading of the circulation may have started a tear in the ventricular wall, already weakened by an infarct; the normal contractions of the ventricle may then have extended this tear from within outwards, and the asphyxia due to the concomitant bronchopneumonia may have constituted a third factor, which acted by causing dilatation of the right ventricle and thinning of its wall.

In the case presented here the very small size of the perforation in the right atrium made it unlikely that the degeneration of the atrial myocardium was due to infarction. Moreover, in serial sections taken through the tissue on each side of the perforation, no evidence of occlusion or obstruction could be found in the neighbouring blood vessels, nor was there any evidence of haemorrhage or fibrosis in the vicinity of the rupture. The lesion appeared to be a focal hyaline degeneration of the myocardium, the cause of which is not clear. The atrial wall in the newborn infant is so thin that it becomes transparent when the atrium is greatly dilated, and the external surface then appears as a patchwork of dark blue areas separated by the brownish striae of the thicker muscular bundles. In this case myocardial degeneration had occurred at a point where there was only a very thin layer of muscle, so that a weakened area, unable to withstand any increase in the intra-atrial blood pressure, was formed. The presence of subpleural petechiae on the lungs and the considerable degree of cerebral vascular congestion indicate that the foetus was subjected to some degree of anoxia during labour, the origin of which may possibly have been related to the abnormal location of the placenta in one horn of the bicornuate uterus, or to the breech delivery of the foetus.

Since the birth of this stillborn child the mother has had a second living child which, on account of the bicornuate uterus, was delivered at 37 weeks by Caesarean section.

Summary

A case is reported of a stillbirth, in which foetal death was caused by spontaneous perforation of the right atrium with subsequent haemopericardium, shortly before delivery. The rupture occurred at a point where the atrial myocardium had undergone focal hyaline degeneration, no cause for which was found.

This is believed to be the second recorded case of spontaneous haemopericardium occurring in the newborn infant, and the first in which this lesion has been the cause of stillbirth.

I wish to thank Professors James Young and J. H. Dible, for their permission to publish the details of the case, and Dr. J. Murray, for his criticism and advice. My thanks are also due to Mr. E. Clark, F.I.M.L.T., for the photomicrograph.

REFERENCES

Benmussa, S., Caruana, M. and Hamza, B. (1950). *Arch. franç. Pédiat.*, 7, 607.
Diamond, J. L. (1945). *Lancet*, **65**, 396.
Fulton, M. N. (1940). *Med. Clin. N. Amer.*, **24**, 1371.
Knop, C. Q. and Bennett, W. A. (1944). *Proc. Mayo Clin.*, **19**, 574.
Krumbhaar, E. B. and Crowell, C. (1925). *Amer. J. med. Sci.*, **170**, 828.
Lyon, R. A. (1950). In 'Mitchell-Nelson Textbook of Pediatrics', 5th ed. p. 1070. Philadelphia.
Ravich, R. M. and Rosenblatt, P. (1947). *J. Pediat.*, **31**, 266.

RUPTURE OF A MYCOTIC ANEURYSM OF THE THORACIC AORTA

BY

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Aortic aneurysms are rare in childhood. Calvin and Nichamin (1934), in a review of the literature up to 1934 were able to find 44 cases under the age of 18 years. They added two cases of their own. Since this time seven further cases have been reported bringing the total to 53 cases. The patient to be described was first seen 18 months before death and was suffering from streptococcal septicaemia. At that time a radiograph of the chest was normal. The fatal haemoptysis terminating the second admission to hospital occurred from an aortic aneurysm which presumably developed as a consequence of the initial illness.

Case Report

The patient, a girl aged 13 months, was admitted to hospital on October 12, 1948, with a history of feverishness and fretfulness for one month. The day before admission she suddenly became worse, was unable to sit up, manifested pain in the legs when the napkin was changed and ran a high temperature. On examination the child appeared ill. She was irritable, resented handling, and the neck was resistive to flexion. A spotty, purpuric rash was present all over the body, more marked on the buttocks. The temperature was 104° F., pulse rate 150. The heart sounds were closed, and râles were present at both bases. The right knee joint was red, swollen and tender. A presumptive diagnosis of septicaemia with complicating arthritis and meningitis was made.

Laboratory Studies. A blood count on October 12 gave the following results: Haemoglobin, 9·4%; colour index, 0·92; red cells, 3,290,000; white cells, 19,300 (neutrophils 77%, monocytes 2%, lymphocytes 19%, plasma cells 1%, metamyelocytes 1%). The red cells showed anisocytosis and polychromasia. Some polymorphs showed toxic granulation and there was a slight shift to the left.

The cerebrospinal fluid was examined on October 12, and showed 22 polymorphs, 5 lymphocytes and one disintegrated cell per c.mm. No bacteria were detected on direct or cultural examination. Total protein was 35 mg.%, chloride 715 mg.% and sugar 63 mg.%. Three days later the examination was repeated and 2 polymorphs and 2 lymphocytes per c.mm. were present. Occasional erythrocytes were seen. No bacteria were found on direct and cultural examination. Total protein was 40 mg.%, chlorides 725 mg.% and sugar 60 mg.%.

Blood culture on October 12 recovered a non-haemolytic streptococcus.

Agglutination tests for typhoid and paratyphoid were negative on October 14.

A radiograph of the chest on October 13 (Fig. 1) showed that the lungs and heart were normal. The Mantoux test was negative.

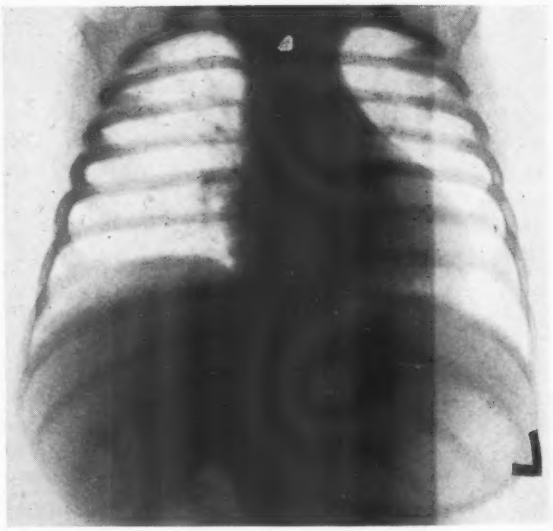

FIG. 1. Radiograph on the first admission showing a normal heart with no evidence of aneurysm.

The child was treated with penicillin, 50,000 units intramuscularly every three hours, with one sulphadiazine tablet, at the same time and half a tablet every four hours. Penicillin, 10,000 units, was given intrathecally on October 16.

The temperature subsided within three days and the child was discharged 10 days after admission. The final diagnosis was streptococcal septicaemia.

The child was re-admitted to hospital on April 24, 1950, at the age of 2 years and 7 months, with a history of having coughed up 2-3 oz. of bright red, frothy blood the previous day. She had been in good health since the previous admission except for frequent attacks of 'bronchitis'. The haemoptysis had occurred without warning and was followed a few hours later by a small haematemesis of presumably swallowed blood.

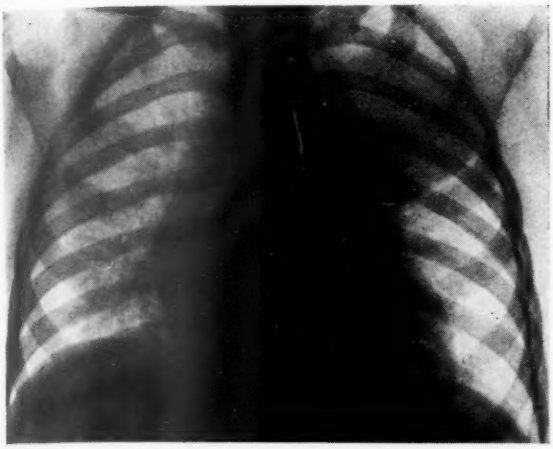

FIG. 2.—Aneurysm of arch of aorta.

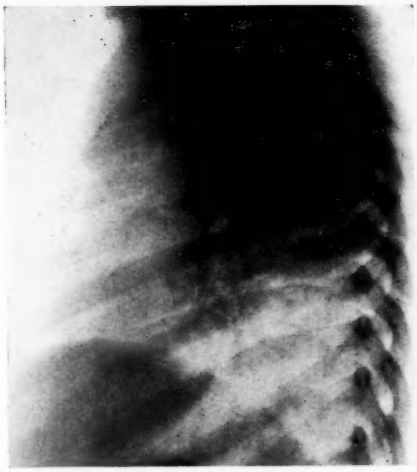

FIG. 3.—Lateral view of aortic aneurysm showing posterior location.

When first seen at the hospital, the child appeared comfortable and not seriously ill. There were loud râles and rhonchi in both sides of the chest. The heart seemed normal, apart from a tachycardia of 140 per minute. However, auscultation was rendered difficult by the loud râles and rhonchi in the chest. The child remained apyrexial and asymptomatic. On the morning of April 27, three days after admission, the lungs were clear on auscultation, except for some coarse crepitations at the left apex. In addition, a fairly loud, blowing, systolic murmur was audible widely over the upper part of the chest on the left side, posteriorly as well as anteriorly. The heart sounds were closed at the apex. Radiographs (Figs. 2 and 3) taken on the previous day showed an opacity with a sharply defined lower edge at the apex of the left lung. This opacity had not been present when the child was radiographed in 1948 during her first stay in hospital. The diagnosis of an angiomatous tumour was mooted and fluoroscopic screening was to be carried out the following morning to define the limits of the mass in the left apex more clearly. However, on the same afternoon, again without any warning, the child coughed up 4-5 oz. of bright red blood.

After the haemoptysis the chest was again filled with coarse crepitations and râles, and the systolic murmur could only be heard anteriorly over the left apex of the lung. On the following morning the child suddenly coughed up a large amount of blood, estimated at several pints, and died within a few minutes.

The following investigations had been carried out after admission: The Mantoux test was negative at 1 : 1,000. The prothrombin index was 97% of normal. A blood count gave haemoglobin 11·2%; colour index, 0·95; red cells, 3,820,000; total white cells, 19,600 per c.mm.; packed cell volume, 33·5%; sedimentation rate 30 mm. in one hour.

The stools contained cysts of *Giardia intestinalis*.

Necropsy. The upper lobe and the upper portion of the lower lobe of the left lung were bound to the posterior thoracic wall by dense, avascular adhesions. Similar adhesions had obliterated the fissure between the left upper and lower lobes. At the apex of the left upper lobe there were some bullous areas which were filled with blood. The rest of the heart and of the lungs was normal on inspection. In the substance of the apex of the left upper lobe, and extending a little into the apex of the lower lobe, a hard, round mass was palpable. This mass was completely surrounded by lung tissue and the dense adhesions just mentioned which glued together the two lobes of the lung. An incision through the apex into the mass (Fig. 4) showed an aneurysm, 1 in. in diameter, which was found to arise from the convexity of the aortic arch, just distal to the origin of the left subclavian artery, the communication being a clean, round hole 2 mm. in diameter. The interior of the aneurysm in the immediate vicinity of the opening into the aorta was covered by normal endothelium. The opposite wall consisted of concentric layers of avascular, organized clot. One portion of the upper wall, which was covered with fresh, ante-mortem clot, had given way and the aneurysm had ruptured into one of the bronchi of the left upper lobe.

The heart was macroscopically normal. There was no evidence of endocarditis. Microscopic sections of the aorta in the region of the aneurysm showed replacement of muscle and elastic tissue by hyaline fibrous tissue (scar tissue). There were no signs of active inflammation or of rheumatic aortitis. The histological features of the sections were thought to be consistent with the diagnosis of old mycotic aneurysm.

Sections of the heart muscle showed no abnormalities.

Discussion

Our diagnosis of mycotic aneurysm was based on circumstantial evidence. The child suffered from an attack of septicaemia 18 months before death. A non-haemolytic streptococcus was recovered from the blood at that time. It is open to speculation whether this, or some other organism which responded to penicillin and/or sulphadiazine, was responsible for the septicaemia. A radiograph taken at the time did not show any signs of an aneurysm and it is presumed that this developed later. There were no signs of syphilis, either

macroscopically or microscopically, in the aorta and the heart. The aneurysm was not found in the situation of a ductus arteriosus. There were no manifestations of sepsis in the structures adjacent to the aorta, which might have led to its erosion. Finally, there was no sign of endocarditis.

Bronson and Sutherland (1918) quote the following aetiological factors in aneurysm formation in childhood: (1) atheromatous degeneration, (2) trauma, (3) erosion of the aorta from without, (4) congenital malformation, (5) acute infectious diseases. They consider the last group to be the most important one.

Calvin and Nichamin (1934) state that in their series of 44 cases there was 'an association with endocarditis in 10, and with rheumatic fever in 11 instances'. They continue:

> 'The predominance of rheumatic fever as an etiological factor in the production of aortic aneurysms in the young is thus apparent from a review of the literature, almost half of all the reported cases being in the rheumatic fever group.'

From a perusal of a number of case reports we have been left with considerable doubts whether some of the authors have not labelled their cases 'syphilitic' or 'rheumatic' occasionally with very little justification for such a diagnosis.

In three of the seven cases reported since 1943 the diagnosis seems to be well established. In Nicholson's (1940) case there was a calcified mycotic aneurysm associated with coarctation of the aorta and an arrested subacute bacterial endocarditis. Baer, Taussig and Oppenheimer (1943) demonstrated cystic spaces containing a coagulum in the media of the aorta in parts not affected by the aneurysm. The latter was due to a weakening of the aortic wall by these cystic spaces. The patient was also suffering from arachnodactyly and multiple congenital cardiac defects. Identical lesions in the media of the aorta have been reported in other cases of arachnodactyly. In McLaurin's (1945) case a dissecting aneurysm had originated in an atheromatous patch of the aorta. The kidneys showed evidence of subacute and chronic glomerulo-nephritis and the condition was probably secondary to hypertension.

Mycotic aneurysms 'metastatic' in nature, that is, neither caused by extension from suppurating neighbouring structures nor associated with bacterial endocarditis, are very rare indeed. Revell (1945), when discussing this type of aneurysm occurring in any of the arteries and at all ages, was able to list only 23 reports in the medical literature. To these he added a case of his own. The youngest patient was $10\frac{1}{2}$ years old. This type of aneurysm, rare though it is, seems to have a definite predilection for the thoracic aorta. In 11 of the cases the ascending aorta was the seat of the aneurysm. The arch was involved in five cases and the descending aorta in two cases. The abdominal aorta was affected five times and other arteries in the body seven times. In six cases two or more aneurysms were present in the same individual.

FIG. 4.—Necropsy specimen showing aneurysm 1 in. in diameter.

Summary

Fatal haemorrhage occurred in a child aged 2 years and 7 months from the rupture of an aneurysm of the aortic arch, probably mycotic in origin, into a bronchus of the left upper lobe of the lung. The aetiology of aortic aneurysm in childhood is discussed. The apparent predilection of mycotic aneurysm for the thoracic aorta is pointed out.

REFERENCES

Baer, R. W., Taussig, H. B. and Oppenheimer, E. H. (1943). *Bull. Johns Hopk. Hosp.*, **72**, 309.
Bronson, E. and Sutherland, G. A. (1918). *Brit. J. Child. Dis.*, **15**, 241. Cited by Calvin and Nichamin.
Calvin, J. K. and Nichamin, S. J. (1934). *Amer. J. Dis. Child.*, **48**, 780.
McLaurin, J. W. (1945). *New Orleans med. surg. J.*, **97**, 317.
Nicolson, G. H. B. (1940). *Amer. Heart J.*, **20**, 357.
Revell, S. T. R.(1945). *Ann. intern. Med.*, **22**, 431.

BRITISH PAEDIATRIC ASSOCIATION

PROCEEDINGS OF THE TWENTY-THIRD GENERAL MEETING

The twenty-third annual meeting of the British Paediatric Association was held at Windermere on April 30 and May 1 and 2, 1952.

BUSINESS PROCEEDINGS. The President, Professor N. B. Capon, was in the chair and the following members were present:

Drs. F. M. B. Allen, E. C. Allibone, J. Apley, I. Anderson, H. T. Ashby, H. S. Baar, H. Stanley Banks, T. E. D. Beavan, J. M. Bligh, M. Bodian, R. E. Bonham Carter, F. Braid, J. V. Braithwaite, D. Browne, H. C. Cameron, W. A. B. Campbell, N. B. Capon, I. A. B. Cathie, W. R. F. Collis, T. Colver, B. D. Corner, D. Court, J. Craig, W. S. Craig, E. M. Creak, J. Crooks, V. M. Crosse, G. Davison, R. Debré, R. H. Dobbs, E. Dott, S. A. Doxiadis, R. W. B. Ellis, J. L. Emery, P. R. Evans, F. J. Ford, A. W. Franklin, D. Gairdner, W. F. Gaisford, R. R. Gordon, S. Graham, C. F. Harris, E. W. Hart, J. Hart-Mercer, J. D. Hay, J. L. Henderson, A. Holzel, D. V. Hubble, J. H. Hutchison, R. S. Illingworth, N. M. Jacoby, H. Everley Jones, R. Lightwood, P. MacArthur, D. MacCarthy, A. MacGregor, H. M. M. Mackay, R. MacKeith, R. A. McCance, C. McNeil, A. G. Maitland-Jones, A. A. Moncrieff, A. V. Neale, G. H. Newns, D. N. Nicholson, J. N. O'Reilly, C. G. Parsons, W. W. Payne, C. B. Perry, C. T. Potter, B. Schlesinger, R. A. Shanks, W. Sheldon, U. Shelley, V. Smallpiece, W. C. Smallwood, J. M. Smellie, J. F. Smith, R. E. Smith, Sir James Spence, R. E. Steen, K. Tallerman, M. L. Thomson, R. McL. Todd, C. W. Vining, H. K. Waller, A. G. Watkins, H. P. Williams, T. P. Williams, M. J. Wilmers, D. W. Winnicott, W. F. Young, S. Yudkin, R. B. Zachary.

The Association had the honour of entertaining Professor Robert Debré, of Paris, who gave the Windermere Lecture, and 50 guests.

The minutes of the last annual general meeting were approved.

The following alterations in rules were moved on behalf of the executive committee and carried *nem. con.*: (alterations are in italics).

RULE 3 to read: The business of the Association shall be conducted by an Executive Committee, consisting of a President, a Treasurer, a Secretary and *twelve* Ordinary Members. All these officers shall be elected at an Annual General Meeting.

RULE 4 (part of) to read: The *twelve* Ordinary Members shall hold office for *three* years. *Four* shall retire annually and shall not be eligible for re-election until after the lapse of three years. Not more than two of the *twelve* Ordinary Members of the Committee shall be resident in any one town, except in the case of London.

RULE 5 (to replace old Rule 6) to read: The Executive Committee shall have power to set up sub-committees from time to time and, for this purpose, may co-opt members of the Association other than those on the Executive Committee and also such other interested persons as they may deem advisable. The Executive shall appoint *from among its members* a Chairman of each sub-committee.

RULE 8 (old Rule 9) to read: The Executive Committee shall be responsible for the arrangements of the General Meeting, and shall meet at such times as may be convenient. *Six* shall form a quorum. It shall be part of its duties to consider the names of all candidates proposed for election to the Membership of the Association and to nominate to the General body of Members such candidates for election as it may consider desirable.

Rules 5 onwards have been renumbered because old Rule 5 has now been taken into Rule 4.

RULE 11 (old Rule 12) to omit: Two such Members may be elected annually.

ELECTION OF OFFICERS. The following were elected by ballot for the year 1952-53.

PRESIDENT. Professor J. M. Smellie.
TREASURER. Dr. R. C. Lightwood.
SECRETARY. Professor Alan Moncrieff.

EXECUTIVE COMMITTEE (new members):
Dr. D. Court
Professor J. Craig
Professor W. S. Craig
Dr. D. Gairdner
Professor W. Gaisford
Dr. R. E. Steen

ELECTION OF NEW MEMBERS. The following were elected by ballot to membership of the Association:

(a) HONORARY MEMBERS:
Professor N. B. Capon
Dr. P. Henderson

(b) ORDINARY MEMBERS:
Dr. J. Apley (Bath)
Dr. N. S. Clark (Aberdeen)
Miss Isabella Forshall (Liverpool)
Dr. A. Holzel (Manchester)
Dr. D. McCarthy (Aylesbury)
Dr. S. Yudkin (London)

The TREASURER'S REPORT was received and approved.

The REPORT OF THE EXECUTIVE COMMITTEE was received and approved and is printed below.

NEXT MEETING. A proposal to visit Porthcawl was discussed, and, as an informal vote indicated an almost exact division of members between accepting this or returning to Windermere, the matter was left to the Executive Committee.

Report of the Executive Committee 1951-52

1. The Association will wish to congratulate Sir Robert Hutchison on his eightieth birthday and Dr. Donald Paterson on his election as Clinical Professor in the Department of Paediatrics in the Faculty of Medicine of the University of British Columbia.

2. The Executive Committee has met on three occasions since the last Annual General Meeting in Windermere in April, 1951, and some account of the business transacted is summarized in this report.

3. VISIT OF DUTCH PAEDIATRICIANS. Many letters of thanks were received after last year's meeting and the gift of an episcope from the Dutch visitors to the Association was much appreciated. The old lantern has now been sold and a diascope attachment purchased for the new machine which will be in use for the first time at the 1952 meeting.

4. LEONARD PARSONS MEMORIAL FUND. It has been decided to open a special fund for the Association and, as a recent circular indicated, ideas for the form of the memorial have been invited.

5. INTERNATIONAL PAEDIATRIC CONGRESS. Few details regarding the 1953 Congress are available. It will be held in Havana, opening on October 12 and lasting three to four days. There are to be five plenary sessions and a scientific exhibition, but no private communications. A series of simultaneous 'Round Table Discussions' is being arranged. No success has yet been obtained in securing transport by a chartered ship. It may be necessary for the Association to subscribe funds to send a delegate to the meeting.

6. ARCHIVES OF DISEASE IN CHILDHOOD. It was recommended to the Editorial Committee that Dr. John Craig and Dr. Kenneth Tallerman should replace Dr. A. W. Franklin and Mr. T. T. Higgins for 1952; and that Mr. Mason Brown and Mr. R. B. Zachary should replace Professor S. Graham and Professor Alan Moncrieff for 1953.

7. CONVALESCENT HOMES. The Sub-Committee has met four times during the year and has arranged two pilot surveys to be carried out on the results and type of convalescence in children. Members of the Association are asked to assist this committee in providing criteria on which to judge the value of convalescence and the average time necessary after various diseases.

8. PREMATURITY. The joint standing committee with the Royal College of Obstetrics and Gynaecology has continued to meet. The report on the care of the premature baby was published in the June, 1951, issue of the *Archives of Disease in Childhood* and proved so popular that after all available reprints had been distributed the Ministry of Health asked for permission to have further copies duplicated to deal with many requests received. An investigation into the aetiology of retrolental fibroplasia has been started by the Medical Research Council at the instigation of the joint committee. An enquiry into the most profitable lines of investigation into the causes of prematurity has been started and three additional members have been appointed by the R.C.O.G. on account of this; particular attention will be paid to the prevention of birth injury and asphyxia in the premature baby. Professor W. Gaisford has been nominated to a steering committee investigating certain aspects of premature delivery and work during pregnancy, sponsored by the National Birthday Trust.

9. ALTERATION IN RULES. The Executive Committee has given careful consideration to the constitution of this committee and its relation to various sub-committees. Alterations in rules have been agreed upon and are being proposed at the Annual Meeting.

10. SENIOR REGISTRARS. After information had been obtained from each region on the minimum number of additional consultant posts in paediatrics required to give an adequate paediatric service, a strongly-worded protest was drawn up and sent to the Ministry of Health on the small number of senior registrar posts in paediatrics which had been actually allocated.

11. PARIS MEETING. An invitation was received for a limited number of members to attend a meeting in Paris of the Association of Paediatricians of the French language, and the Paediatric Section of the Royal Society of Medicine received a similar invitation from the Paediatric Society of Paris. Arrangements have been made to accept this invitation.

12. WINTER MEETING. A request was received for a winter meeting in London and it was decided to discuss this informally during the Annual Meeting and reconsider it again in the autumn.

13. CENTRAL MIDWIVES BOARD. The Executive Committee has noted with satisfaction the election of a paediatrician as vice-chairman of the Central Midwives Board.

14. OTHER ACTIVITIES. The sub-committees which prepared a memorandum for the Ministry of Education on the maladjusted child gave verbal evidence before the special committee in September, 1951. The secretary attended a meeting in Zurich during October to discuss paediatric abstracts, but the deliberations were mostly concerned with the provision of abstracts outside the English-speaking world. The Executive Committee has under consideration the purchase of a presidential badge. Inquiries during the year which were dealt with by the Committee or by the officers included one from the Ministry of Health on poisoning by nitrites in drinking water and another on evidence concerning the relation of milk prices and quality.

15. The Executive Committee has welcomed Dr. Dorothy Taylor as observer from the Ministry of Health in place of Dr. G. I. Brodie who has retired.

16. The Association has heard with sorrow of the deaths of Dr. H. Chodak Gregory, an honorary member, and of Professor Geoffrey Fleming, original member and past president.

Scientific Communications

Professor Robert Debré, of Paris, delivered the Windermere Lecture for 1952 entitled 'Miliary Tuberculosis'.

DR. A. D. BARLOW, introduced by Dr. B. E. Schlesinger, F.R.C.P., 'Antidiuretic Substances in the Blood in Nephrosis'. Heparinized plasma from the antecubital veins of normal children has no antidiuretic effect when injected subcutaneously or intravenously into rats. Plasma from an internal jugular vein has antidiuretic activity which varies with the state of hydration of the child from which it was taken.

Plasma from the antecubital veins of five children with Type II nephritis (Ellis) was strongly antidiuretic.

It is unlikely that the substance in the peripheral blood of these nephrotic children is the antidiuretic hormone of the posterior lobe of the pituitary. If it were vasopressin, there would be levels equivalent to 0·1-0·2 m.u./ml. plasma, and in the presence of so much, it seems unlikely that a small injection of posterior lobe extract would have any further effect. A slow intravenous injection of a few m.u. vasopressin does, in fact, reduce the rate of urine flow in Type II nephritis.

The antidiuretic tests have been performed by Dr. S. E. Dicker using the method of Dicker and Ginsberg (*Brit. J. Pharmacol.*, 1950, **5,** 497), and that of Jeffers, Livezey and Austin (*Proc. Soc. exp. Biol., N.Y.*, 1942, **50,** 184).

DR. A. W. FRANKLIN (London). 'Chloramphenicol in the Treatment of Bronchiectasis.' Thirty-two children, 24 severe and eight mild cases, were studied to discover the smallest dosage of chloramphenicol that could help children with bronchiectasis, cutting cost and the risk of moniliasis. The bacteriological investigations were made by Professor L. P. Garrod and his assistant, Miss Waterworth. Twenty cases, aged 5 to 10 years, in the Meath School of Recovery at Ottershaw, and 11 older children were given varying doses of the drug by mouth. *H. influenzae* was present in all sputa and alone in 14. Doses of 20-30 mg. per lb. daily given in three eight-hourly parts, caused dramatic lessening of the quantity of sputum on the third or fourth day and sterilization of the sputum on the sixth day. Although bacteria usually returned within 10 days of ending treatment, in mild cases symptoms were minimal for periods of weeks. Several courses of treatment could be given to the same child without loss of effectiveness. With less than 20 mg. per lb. per day infection was not controlled. A weekly dose of 20-30 mg. per lb. given in three doses on one day produced a sterile sputum on the day following but the occasional *H. influenzae* later in the week. Acute febrile illness may follow sudden withdrawal of full doses. *In vitro* bacteriological findings suggest that *H. influenzae* remain sensitive to concentrations of 1·0 μg. per ml. even after several courses of treatment without developing resistance. Pneumococci required concentrations of 2·5 or 5 μg., rising to 10 and 15 μg. per ml. as time passed. Staphylococci were only found late, and in seven such cases required the high concentration of 50 μg. per ml. Chloramphenicol has a real value for bronchiectatics before operation on the upper or lower respiratory tract, bronchoscopy and bronchography. Secondly, the drug may, if used in the treatment of infant pneumonia, primary or complicating whooping cough, or pink disease, prevent the initial infection. Thirdly, mild unilobar cases with tubular dilatation may be kept for long periods in good health and on full activity with occasional doses or courses of treatment. Fourthly, in the severe disabling cases, periodical courses of treatment may give the unfortunate patient periods of respite from the most unpleasant features of the disease.

DR. DONALD COURT. 'The Extent and Character of Whooping Cough in Newcastle upon Tyne, 1947-1951.' For the past four years, the character and spread of whooping cough has been studied in 919 representative families in the city. The disease has been continuously present without showing epidemic tendencies. Its progression through the

group has been remarkably regular, and of the 919 children, 314 (34%) had had whooping cough by their fourth birthday. Five per cent had started the disease before they were 6 months old. Family infectivity was high, with eight out of 10 susceptibles contracting the disease. A watery nasal discharge was present from the beginning, and in some for several days before the cough, in over half of the children. Although the cough has no specific characteristics in the first week, it is more severe than one would expect from the nasal discharge alone, and this disproportion is a help in early diagnosis. Whooping was only present in 64%. Paroxysmal sneezing dominated the picture in the first two weeks in 13 children. Wheezing was notably absent even in asthmatic children.

The main query, however, concerned the clinical consistency of the disease. Our experience is similar to that of the Medical Research Council (*Brit. med. J.*, 1951, **1**, 1483), and suggests that although there are considerable variations in the intensity of the disease, the traditional picture can be recognized in over 90% of cases, and the marginal fringe of mild or atypical pertussis is small. Among the 314 affected children, there were six pneumonias with three deaths. All the deaths occurred in the first year of life. Two children have segmental collapse which has lasted for more than 18 months, without clinical bronchiectasis.

Although the complications appear less formidable when set in the total context of the disease, the distressing nature of the illness makes prevention a desirable procedure in early childhood, if it can be done with safety.

DR. R. A. MCCANCE (with Nathalie Naylor). 'The Excretion of Administered Water by Young Infants.' After eight to 12 hours without fluid adults and infants (6-39 days old) were given 5% of their body weight of water. Adults excreted a volume equal to this within six hours whereas infants excreted only 60% of the dose before the urine flow subsided. In both adults and infants the peak of the urine flow was one and a half to two hours after the water had been administered. At low rates of flow the urine of the infants was much less concentrated (in terms of m.osmols/litre) than that of the adults. At high rates of flow there was little, if any, difference in concentration between the urines of the adults and infants. Interference with the infants checked the flow and in one case attempts to take blood were followed by a large but temporary fall in flow rate and rise in urine concentration. This effect was probably produced by a release of post-pituitary hormone and indicates that the kidney of some infants can respond well to the hormone, given the appropriate stimulus and conditions.

MR. I. J. CARRÉ (Birmingham). 'The Natural History of the "Short Oesophagus" in Childhood.' A review of the literature on the subject of the 'short oesophagus' and partial thoracic stomach in childhood tended to convey the impression that the condition was uncommon and that the development of an oesophageal stricture was of frequent occurrence.

Yet during 1951, 18 cases were diagnosed in infancy at the Birmingham Children's Hospital. As there was no reason to expect a recent increase in the condition many cases unrecognized in the past must have subsequently remained asymptomatic. These deductions received support from a follow-up of patients attending the Birmingham Children's Hospital between 1940 and 1950. Forty-five previously unrecognized cases had been brought to light. Nearly all of them were free of symptoms when seen.

A total of 111 radiologically diagnosed cases had been studied at the Birmingham Children's Hospital. A review of the clinical histories of the older children suggested that a useful guide to the future progress might be the effect on symptoms of weaning to solids. Sixty cases for which adequate detailed clinical histories were available had been followed up for over two years since the onset of symptoms. These were divided into two groups on the following basis of the effect of weaning: (1) improvement, (2) no change or worse.

On analysis it was found that in children belonging to Group 1 the condition was essentially benign and that the symptoms had usually ceased by the age of 2 years without recurrence in later years. In Group 2, on the other hand, the majority of children had persistent symptoms, i.e. daily vomiting, periodic vomiting attacks or dysphagia, up to 4 years or so, and in many instances for considerably longer. Within this latter group also fell all the cases which developed complicating oesophageal strictures. These observations confirmed, therefore, that the effect of weaning onto solids provides a useful guide to the future course of the condition in childhood. They also served to differentiate three clear-cut clinical types. The relative proportion of all cases falling into each of these types was assessed as follows: Benign asymptomatic clinical course, 75%; prolonged course with persistence of symptoms, 20%; development of complicating oesophageal stricture, 5%.

DR. BERYL D. CORNER (Bristol). 'Lipoatrophic Diabetes.' The association of diabetes mellitus and portal cirrhosis with the rare condition of

generalized lipodystrophy has occasionally been described. Lawrence (1946) in suggesting the name lipoatrophic diabetes emphasized the lack of ketosis, and the presence of normal plasma insulin and pancreatic islet tissue. A case was described of a 14-year-old girl who had progressive generalized lipodystrophy since pertussis at 10 months of age. When first investigated she was symptom-free and well developed, but had not menstruated. Her muscles were strikingly powerful. Blood pressure was persistently raised and there was moderate albuminuria. Blood plasma was lipaemic with 3·5 g./100 ml. total lipids, but sugar and insulin tolerance were normal. A right abdominal swelling proved at laparotomy to be a large but otherwise normal kidney, and a moderately enlarged liver, a biopsy of which showed early portal cirrhosis with heavy fat infiltration of liver cells and normal glycogen content. Three months later heavy glycosuria and hyperglycaemia appeared which rapidly became insulin-resistant. During the 18 months of observation there had never been ketosis, the fasting lipaemia had increased to 6·9 g./100 ml. and the liver had rapidly enlarged to below the umbilicus. The B.M.R. is +45% in the absence of signs of thyrotoxicosis and the respiratory quotient is low. Despite the signs the patient feels fit and continues normal activity.

The whole problem of fat metabolism is raised by this case. The low respiratory quotient and lack of ketosis suggest that fat is being excessively but efficiently oxidized, and the muscle metabolism would seem adequate.

It seems unlikely that the lipaemia is entirely due to circulating ingested fat, therefore it is possible that liponeogenesis from carbohydrate is proceeding but that an unknown enzyme mechanism of retention of fat in adipose tissue has failed, so the excess lipids eventually choke the liver and produce cirrhosis. Only at this stage does the utilization of carbohydrate become impaired owing to the excessive demands for metabolism of fat. Hence hyperglycaemia, which cannot be controlled by insulin, develops.

Dr. J. L. Emery (with H. B. Stonier and H. J. Whitely) (Sheffield). 'Observation on the Activity of the Adrenal in the Newborn.' Cytochemical studies had been carried out on 72 newborn and stillborn infants. Based on size, shape and distribution of doubly refractile and fatty material in the 'adult' cortex two types of response were seen: (1) complete discharge of lipids, (2) partial discharge with continued activity.

Sixty-one infants dying aged 2 days and under, showed no response of the cortex. The youngest child showing response was aged 4 days. An increasing proportion showed response over that age.

The response in the very young child tended to be discharge rather than continued activity.

Based on a large series of routine adrenals it was found that the thickness of the 'adult' cortex increased slowly in the first 4 days of life, it then grew extremely rapidly for a period of about a week and following this remained fairly stable for many months.

Complete discharge and inactivity of the adrenal cortex in children given 'eucortone' was demonstrated and also hyperplasia when A.C.T.H. was given.

When related to published work on the excretion of ketosteroids and corticoids and the response to A.C.T.H. in the newborn, the findings suggested that the newborn adrenal was held in check in the first few days of life by the corticoids that it had received from the mother. When these had been eliminated a rapid growth of the cortex occurred.

The clinical administration of corticoids in the newborn was likely to postpone the growth of the adrenal cortex, and, unless a stimulant to growth such as A.C.T.H. were given, a severe developmental endocrine imbalance might occur.

Dr. R. McL. Todd (Liverpool). 'The Treatment of Primary Pulmonary Tuberculosis with Para-Amino-Salicylic Acid.'

Sixty-nine children with primary pulmonary tuberculosis were admitted to hospital during 1951 and for the purposes of this investigation the patients were divided into four age periods (0 to 1 year, 1 to 3 years, 3 to 7 years and 7 to 15 years). Alternate ('trial') patients in each age group received 0·5 g. para-amino-salicylic acid (P.A.S.) per lb. weight daily for three months, while the remaining patients ('control') received no specific therapy. All patients were in hospital for three months and were given adequate rest, diet and vitamins.

In 70% of the cases in the trial group and in 80% of the control group the estimated age of the primary complex was three months or less, and in other respects (contact history, positive gastric lavage, x-ray appearances) the trial and control groups were comparable.

Progress was assessed clinically, by serial blood counts, sedimentation rates, radiographs and by weight gain. These criteria provided evidence of similar progress in the two groups. Complications developed in 10 patients in the trial group and eight in the control group, the most serious being tuberculous meningitis in two children (control group), miliary tuberculosis in one child (control), renal tuberculosis in one child (trial), tuberculous

peritonitis in one child (trial), and all these children were under the age of 4 years. Other complications were extension of the local pulmonary lesion, gastro-enteritis and P.A.S. sensitivity.

It was concluded that P.A.S. was of little or no value in the treatment of primary pulmonary tuberculosis in children over the age of 3 years. In infants under this age, because of the frequency of generalized complications, it would seem reasonable to give streptomycin and P.A.S.

DR. P. MACARTHUR (Glasgow). 'Foetal Vaccinia and Vaccinia Gravidarum.' A healthy young woman, who had a primary vaccination when three months pregnant, was spontaneously delivered of a premature infant three months later. The infant was suffering from generalized vaccinia, acquired *in utero*, and died 15 hours after birth. The diagnostic investigations were described and the case was compared with the only previous recorded example of foetal vaccinia (Lynch, 1932).

The recognition of this case led to further enquiries to establish the frequency with which vaccination during pregnancy had a harmful effect on the foetus. These enquiries were described. The outcome of 203 pregnancies in women who were successfully vaccinated during pregnancy was analysed and the incidence of foetal loss was compared with that which might occur in a normal, unvaccinated series. Statistical analysis of the results showed that there was a highly significant increased mortality among the foetuses of women who were vaccinated during the first trimester of pregnancy.

It was suggested that women should never be vaccinated during the first trimester of pregnancy as part of routine public protection and that these women should be vaccinated only if they had been in contact with a case of smallpox.

DR. O. WOLFF (with Dr. W. C. SMALLWOOD, Birmingham). 'The Effects of Meningococcal Meningitis on the Intelligence and the Hearing.' The survey is of cases treated from 1937 to 1943 and from 1946 to 1949. During this period 179 children were discharged from the Birmingham Children's Hospital having survived an attack of meningococcal meningitis.

One hundred and thirty-eight (80%) were re-examined. The shortest time interval which elapsed between the attack and the re-examination was approximately two years.

The mean intelligence quotient of the 26 children whose attack occurred under the age of 6 months was 76·3; 15% of this group had quotients of 30 or under, i.e. they were idiots.

The mean intelligence quotient of the 27 children whose attack recurred during the second six months of life was 90·8.

The mean intelligence quotient of the 81 children whose attack occurred over the age of 1 was 96·8. This mean does not differ significantly from the normal mean of 100.

Complete audiographic tests were performed on 124 children. In 26 instances (approximately 20%) there was evidence of nerve deafness; in only three of these was the hearing loss sufficiently severe to warrant admission to a deaf school.

Of the children whose attack of meningitis occurred under the age of 1 the hearing was impaired in 28% of cases while of the children who had the attack over the age of 1 only 16·6% suffered hearing loss.

Impairment of the intelligence and the hearing is not uncommon following an attack of meningococcal meningitis in the first year of life.

DR. W. W. PAYNE (London). 'The Blood Chemistry in Idiopathic Hypercalcaemia.' Besides the raised blood calcium and urea and the normal phosphate, phosphatase, chloride and bicarbonate, there was in these cases a raised plasma protein, the α_2 and γ globulins being increased. The increase in the serum calcium occurred in the ultra-filtratable fraction but the cerebrospinal fluid calcium was normal. The daily calcium and phosphorus retention was normal. The urinary calcium was low early in the disease but later rose to just above normal. The renal function was depressed in the active phase but returned to normal in convalescence.

The cause was discussed and it was concluded that neither hyperparathyroidism nor hypervitaminosis D and none of the other known causes of a raised calcium could adequately account for all the findings.

DR. REGINALD LIGHTWOOD (London). 'Idiopathic Hypercalcaemia in Infants with Failure to Thrive.' In a previous study of 31 infants with primary renal acidosis, hypercalcaemia occurred in two. Attention was then given to the clinical features of 10 hypercalcaemic infants without concurrent renal acidosis forming an apparently homogeneous and 'idiopathic' group. They did well until 3-7 months when symptoms began, anorexia, vomiting, wasting and constipation, suggesting a diagnosis of renal acidosis. The physical state also matched this condition, marasmus, hypotonia and faecal masses often felt per abdomen, although the hypercalcaemic infants were even more constipated and rather more alert. Dehydration occurred in about one half, also thirst, polyuria and spikes of fever. The blood urea was increased. After lasting from five months

to more than 15, slow spontaneous recovery took place, though only after the return to normal of the calcium and urea levels; sometimes, however, a short secondary rise in the serum calcium occurred.

Since leucocytes, epithelial cells and sometimes bacteria might appear in the urine, pyelonephritis was often considered but the clinical condition was not materially altered by treatment for pyelonephritis and so any infection was probably acquired secondarily. X-ray examination showed nephrocalcinosis in two infants.

Clinically the cases were indistinguishable from renal acidosis, the differential diagnosis being actually made by examining the urine and blood.

DR. J. O. CRAIG (Birmingham). 'Accidental Poisoning in Childhood.' The communication was a record of 482 cases of poisoning in childhood occurring in the period 1930-1951. Two hundred and fifty-six cases were seen at the Royal Hospital for Sick Children, Edinburgh, and 226 in the Royal Aberdeen Hospital for Sick Children. The work on the Aberdeen cases was done by Dr. M. S. Fraser. Cases of coal gas poisoning and 'food poisoning' were excluded.

Poisoning commonly occurs between the ages of 1 year and 4 years. The sex incidence shows a male : female ratio of 1·46 : 1.

It was shown that the rise in poisoning cases seen at each centre had been fivefold over the period of study. It could not be assumed that this reflected the number of cases of poisoning that occurred in the general population, but it stressed the importance of accidental poisoning to those working in hospital.

The main group of poisons to cause trouble was the 'medicine' group. The fatalities occurring in the whole of Scotland were discussed, and the importance of ferrous sulphate, both numerically and in the production of severe symptoms, was emphasized. Certain points were discussed in detail. The importance of pneumonia in kerosene poisoning was stressed, and also the occurrence of convulsions in camphor poisoning. It was pointed out that barbiturate poisoning often manifested itself with excitement. The antihistamines were mentioned. Attention was drawn to the possible dangers of boric acid as a local application in cases of napkin dermatitis.

DR. FRANK FALKNER (London). 'Measurement in Growth and Development Studies.' Scientists of many branches required information on growth; the doctor specially required to know if a child was growing normally. There was a lack of proper data and national studies were needed with international co-operation. Growth was a highly complex form of movement. There were two basic methods of studying it: the cross-sectional, or distance, study where many individuals were measured at different ages, and the longitudinal, or velocity, method, where the same individuals were measured, ideally from birth to maturity. To know the pattern and rate of growth was more valuable than knowledge of the point of growth reached. Three up-to-date cross-sectional sets of data on height and weight were available in this country but all were open to some criticism. No 'longitudinal' data were available here, but three such studies were in progress.

Height and weight did not indicate the distribution of fat, muscle or bone, which all grew at different rates, nor body build. The necessity of anthropometric measurements other than these two was stressed and a plea made for accuracy. The complexity of growth required that, in every detailed study, estimations be made of bone and mental development, and of biochemical and endocrine changes. Recording of genetic, disease, nutritional and environmental influences was necessary.

Experimental lines of research into growth were discussed together with the application of somatotyping as a method of denoting body-type. There was, as yet, no simple satisfactory test of normal growth in the human child.

BOOK REVIEWS

The Urology of Childhood. By T. TWISTINGTON HIGGINS, D. INNES WILLIAMS and D. F. ELLISON NASH. (Pp. 286; 136 figures. 45*s*.) London: Butterworth and Co. Ltd. 1951.

The publication of this book is an important event in the development of surgical knowledge in this country. The cases of which it treats form a small proportion of the surgical ills affecting the population in general: their pathology is often extremely difficult to unravel; their treatment a matter of difficulty to decide. Yet among them the surgeon may find some of the most rewarding cases in the whole range of medicine; cases in which the right interpretation of symptoms and the right treatment has meant the avoidance of death or of a lifetime of misery.

Here information is given which is not to be obtained elsewhere, even at the cost of prolonged search through medical periodicals. This information is the fruit of many years of study, experience, and experiment upon the immense mass of cases which pours into The Hospital for Sick Children. There is a class of textbook excellent for its primary purpose of enabling students to pass examinations, in that all known methods of treatment are described in it, yet almost useless for guidance in any particular difficulty since there is no firm direction as to which expedients will work and which will not. This book is not of such a kind; it is confined solely to the description of what the authors have reason to think is the pathology of the conditions discussed and to the methods of treatment which they have found successful; together with accounts of particular cases illustrating general principles. There is a welcome absence of the vague oracular statement which so frequently in medical writing conceals the absence of accurate knowledge and clear thought.

An important point about this book is that it appears capable of indefinite growth. Its authors combine the authority of long experience with the fresh outlook of a younger generation, which is as it should be in surgery; and one can hope that editions will succeed each other in which the same balance will be kept. In this way a steadily accumulating but carefully sifted mass of knowledge should always be available to those who are interested. Its readers should include not only urological specialists, but all who have to do with children, whether as physicians, psychologists, or general practitioners. The latter two classes will find one of their commoner and more exasperating problems, that of enuresis, clearly analysed, and principles for its treatment set out in a most helpful way.

A criticism is that more detailed descriptions of technique and instruments might be given. The apparatus needed is so delicate and expensive, and the manipulative skill required so great, that it is difficult to avoid the conclusion that work of this kind should be treated as is cerebral surgery, and concentrated in a few special centres. Finally, in a work that treats of hypospadias and hermaphroditism, it seems illogical to omit to give guidance on a subject upon which most contradictory teaching and practice is in vogue, that of ' undescended testicle '.

Clinical Pediatric Urology. By MEREDITH CAMPBELL. (Pp. 1113; 543 figures. 90*s*.) London: W. B. Saunders. 1951.

Dr. Meredith Campbell's numerous contributions to the literature have already made us familiar with his encyclopaedic knowledge of children's urology, and the appearance of this book, epitomizing his long experience, is an important event for those with a special interest in this branch of surgery. His previous two-volume monograph, *Pediatric Urology*, which appeared in 1937, has been the standard work of reference on its subject: the present work, although very much more than a new edition, follows the same lines and is like its predecessor an invaluable source of information regarding the rarer disorders of the urinary tract. The incorporation of the word ' clinical ' in the title has not unfortunately involved the rearrangement of the material along strictly clinical lines, and the reader may well find it hard to discover Dr. Campbell's opinion upon some of the simpler issues. Even such a clear-cut clinical entity as the pelvic hydronephrosis of childhood is discussed in no less than five separate sections according to its exact cause, which may be discoverable only at operation. Apart from the chapter on urinary infections, which should be of considerable interest to paediatricians, the book will be chiefly of value to surgeons with urological experience. There is a complete range of admirably reproduced pyelograms illustrating every topic, good cystoscopic drawings and an unusually full bibliography. Inevitably there are points upon which other urologists will differ from the author: many will doubt whether they have frequently observed ' advanced prostatitis ' resulting from masturbation or whether meatotomy is invariably required for meatal ulceration, and it seems unnecessary to have included so much discussion of disorders which are exceptionally rare in children yet familiar enough in adult practice. These are of course minor points and in no way affect the importance of the book as a contribution to the literature of urology: both author and publisher are to be congratulated on its production.

An Atlas of General Affections of the Skeleton. By SIR THOMAS FAIRBANK. (Pp. 411. 55*s*.) Edinburgh: E. and S. Livingstone. 1951.

The high standard of medical literature which was expected to appear in Sir Thomas Fairbank's book is now before us. No one can be otherwise than delighted that our very distinguished orthopaedic surgeon has set down his great practical knowledge of the general affections of the skeleton. We shall be more than grateful for this ' information gleaned from my collection of records, a collection accumulated over a period of

many years '. Few are privileged to write so authoritatively on the clinical and pathological aspects of skeletal disease.

The introductory classification of the diseases considered is a revelation of clear thinking and logical arrangement. Sir Thomas has always shown special care in the proper use of words in the nomenclature of diseases in bones and his present list should be accepted as authoritatively correct.

The scheme of presentation adds to the delight of the book, and in nearly every sentence the reader gains something from the fund of personal wisdom displayed and the clinical ideas interpolated gently but persuasively. Not only the core of the subject matter is vividly in focus, but the variations in each particular instance are brought out in an absorbing relevance.

' An Atlas of General Affections of the Skeleton ' will be immediately accepted as a classic in the medical writings of paediatrics. A very large part of the book is related to congenital developmental errors and to problems of nutrition and metabolism. Each chapter is appropriately planned to contain a general discussion on a particular abnormality followed by descriptions and radiological illustrations (and sometimes photographs of the patient) of personally studied cases. Thus the reader is never in doubt of the vast experience incorporated into the book. The historical notes, often serving to introduce the particular syndrome, give further point to the author's sense of responsibility and thoroughness in making known the steps whereby the present status of knowledge has been reached. As an example of the easy power of description, Chapter 32 on renal osteo-dystrophy is recommended for study; all that is known in this extensive field is brought out by the plainest of language in no more than four pages.

The once common diseases, such as infantile rickets, are presented in a refreshingly new way, but by wise action the variety of rickets, e.g. resistant or continued rickets, and some other types of rickets which are relatively more frequently seen at the present time, are given appropriate emphasis both by word and precision in x-ray illustrations. Moreover, in many of the case histories and notes there is an abundance of therapeutic method and prognostic data. It might be fairly stated that Sir Thomas has actually written a series of chapters on the natural history of affections of the skeleton and he has not hesitated to mention, without irrelevance, suitable information on the biochemical findings and on the concurrent physiological derangements. Wherever aetiological factors are doubtful, a skilful discussion usually clears away any pre-existent fogging of ideas.

With commendable brevity the article on Fanconi's syndrome reveals Sir Thomas's great descriptive ability. It is to be noted that he has not necessarily become involved in some of the up-to-date biochemical complexities of renal tubular dysfunction, and it will be necessary to look elsewhere for these. Eosinophilic granuloma of bone is considered in close association with Hand-Schüller-Christian disease and Letterer-Siwe disease, and the radiographs on page 302 clearly show the great similarities in this group. Osseous manifestations in the lipoidoses are well presented. Spinal lesions in Gaucher's disease are shown and some extremely interesting case records are included. Fluorosis and the osteosclerosis due to bismuth, lead and phosphorus receive adequate discussion. The skeleton in the endocrine disorders is a particularly interesting section of the book, and the chapters on pituitary, thyroid and gonadal relationships have a special paediatric interest. The important matter of bone involvement in congenital syphilis is comprehensively illustrated and the radiographs, though demonstrating a little of the common difficulty of reproduction in this particular condition, depict the variety of bone reactions so often helpful in the diagnosis. To throw it into comparative relief, the next chapter is concerned with a classical life history, in text and radiographs, of a case of infantile cortical hyperostosis which, as is usual, reached a favourable conclusion.

The index is another example of precision and completeness.

Pathology of the Fetus and the Newborn. By EDITH L. POTTER. (Pp. 574; 601 figures. 150*s*.) Chicago : The Year Book Publishers Inc. Distributors in Gt. Britain, Interscience Publishers Ltd. 1952.

Dr. Edith Potter has a world-wide reputation as an authority on foetal and neonatal pathology, and this remarkable book is the product of an experience of many years and many thousands of necropsies. It is the work of an author who can draw on a vast store of personal observations and need depend little on secondhand information. An adequate bibliography is given at the end of each chapter, but the text is refreshingly free from references to other people's work: it is very much a record of the author's own experience.

A large proportion of the book is taken up by the description and illustration of malformations. This is done so thoroughly that there can be few developmental anomalies not mentioned, and the pictures provide a gallery of malformations the like of which has probably not been seen before. Errors of development bulk much larger in the book than in the actual practice of foetal and neonatal pathology, but the diseases and injuries that occur during this period of life, and various general aspects of the subject, are not neglected. There are chapters on anoxia, birth trauma, infections, tumours, prematurity, placental pathology and other subjects, as well as references to diseases of the various systems and organs in their appropriate chapters.

A few minor errors have crept in, e.g. the description of the pneumococcus as a Gram-negative diplococcus, and the use of the term ' pyloric sphincter ' where the wall of the pyloric canal is meant. In megacolon, Auerbach's plexus is deficient in the unhypertrophied distal segment, not in the hypertrophied portion as stated. The statement that subdural haemorrhage is uncommon is contrary to general experience, and there is some confusion about the source of subdural bleeding, which on p. 90 is said to be most commonly the middle meningeal artery and on p. 405 the middle cerebral artery—both surprising statements.

The publishers' part in the production of the book is a great achievement. The type is clear and well-spaced;

misprints are few. The illustrations, of which there are over 900 in the 601 figures, all in black and white, are excellently reproduced and contribute immensely to the merit of the book. It is to be regretted that the price has to be so high, but understandable in view of the abundance and excellence of the illustrations.

It is safe to say that this book will immediately be recognized as a classic, and that it will be a long time before a serious rival to it appears.

Foetal and Neonatal Pathology. By J. EDGAR MORISON. (Pp. 366; 59 figures. 50*s*.) London: Butterworth & Co. 1952.

This book is welcome because it is the first on this subject to be published in modern times in this country, and is a notable contribution to a branch of paediatrics and pathology on which few books are available in any language. The author has adopted, where possible, a physiological approach, and the first two parts of the book are devoted to discussion of those factors that may cause disturbance of prenatal life and development, or affect the adaptation of the newborn infant to independent life. This is admirably done, with critical assessment of the present state of knowledge, drawing a careful distinction between what is surely known and what is still largely speculative; and indicating the need for much fundamental research before many of the problems of ' perinatal ' pathology can be solved. There is also a useful section on foetal and neonatal infection.

The descriptions of pathological conditions that may be found at necropsy are given a somewhat subordinate place. They are dispersed among much other matter in the text, and are sometimes too brief to be fully informative to a reader not already familiar with the conditions described. Most of the illustrations are diagrams and charts; only a minority are photographs of pathological material. For these reasons a young pathologist exploring this field as a learner may not always readily find what he needs to guide him as to what to look for in carrying out his necropsies and in the interpretation of what he finds. It is a book to be read right through, rather than used as a textbook of morphological pathology, and everyone interested in the subject will gain much by so reading it. A valuable feature is a large and well chosen bibliography, with important references indicated in heavy type.

Penicillin in Severe Otorhinolaryngological Complications. A Symposium. By ROBERT LUND *et al.* Danish-Norwegian-Swedish Otolaryngological Joint Research. (Pp. 120. $2.50.) Copenhagen: Ejnar Munksgaard. 1950.

The symposium collates the 421 reports collected over the course of one year (1948) from the E.N.T. Departments of the main hospitals of Denmark, Norway and Sweden, the basis of the reports being a questionnaire circularized by a centrally formed committee. Separate chapters by different Danish authors are devoted to the results of penicillin and sulphonamide (essentially sulphathiazole) therapy in the treatment of meningitis, labyrinthitis, cerebral abscesses, petrositis, osteomyelitis, and thrombophlebitis, while the first deals with the bacteriological field and the final chapter lists the allergic and toxic effects encountered.

The results in general confirm the place of penicillin as a great advance in therapy. Though many of the chapters are clearly written, the weight of the evidence from the wealth of material is to a great extent offset by the poorness of the bacteriological control. Of the 421 cases collected, only 182 had bacteriological investigations made, and of these in only 24 (6%) was the sensitivity of the organism concerned determined. Thus many of the statements made in the chapter on bacteriology are not based upon the investigation, and are at considerable variance with those more generally accepted.

Specific Dyslexia (Congenital Word Blindness): A Clinical and Genetic Study. By BERTIL HALLGREN. Translated by ERICA ODELBERG. (Pp. 287. No price.) Copenhagen: Ejnar Munksgaard. 1950.

This study of 169 cases includes only ' specific ' cases of reading difficulty, some seen at the Stockholm Child Guidance Clinic (122 cases), and the rest picked out of a special reading class in a secondary school in Stockholm. Children whose reading difficulty was secondary to emotional disturbance, general backwardness or other causes were excluded. Controls were supplied by non-dyslectic classmates. In the clinic material no child had an I.Q. lower than 80; one school child had an I.Q. of 65-69. Since school starts at the age of 7 and cases were not taken from classes lower than the second, presumably the ages would be around 9 years, and the investigation selected children seen over a period of just under 16 months. The overall estimated incidence for the general population is approximately 10%.

The study is mainly directed to disproving causes popularly associated with this condition, and in supporting the view that it is inherited.

The method of setting out this material is nothing if not detailed and painstaking but the translation is sometimes too literal to clarify the meaning. For example ' in [the author's] opinion, all the forementioned interpretations of the higher incidence of nervous disorders in the probands are plausible. It is, however, extremely difficult to determine the connexion in the individual case. This is especially because the symptoms can have a causal connexion even if it is non-existent.' ' Proband ', a word which does not appear in the *New Oxford English Dictionary*, means by inference a case which is a subject in this enquiry.

The final conclusion is interesting. It has been clinically apparent for a long time that specific dyslexia may have a familial incidence. This enquiry goes into the genetic aspect, supported by very interesting family trees. The author's final positive conclusion states: ' The genetic-statistical analysis shows that specific dyslexia, with a high degree of probability, follows a monohybrid autosomal dominant mode of inheritance ', going on to specify groups in which this is clearly demonstrated by her work.

The overall incidence is high compared with this country, thus throwing open queries as to criteria.

The Feeding of Pre-School Children (Survey of a World Problem). By F. Le Gros Clark. (Pp. 51. 1*s.* 6*d.*) London: National Society of Children's Nurseries. 1951.

The main thesis of this booklet is that preached so often in the last 20 years by Dr. C. D. Williams, of the Colonial Service and of the World Health Organization, namely the crying need throughout so much of the world for better feeding of children between the ages of 12 months and 3 or 4 years of age. The author begins with a consideration of mortality rates among young children in different countries; he contrasts the mortality per 1,000 living in the age group 1-4 years in New Zealand (1·7) or Sweden (2·2) with that of Mexico (48·2) or Egypt (78·9), and compares these again with the much lower mortalities between 5 and 9 years of age (e.g. Mexico 7·9 and Egypt 7·6). He stresses the need for a better diet from the time of weaning as probably the major factor in lowering mortality in this age group, and shows how in many parts of the tropics, the Far East and in Latin America this is bound up with the provision of milk substitute and with the education of parents. Apart from the possibility of increased milk production, the author urges the wide use of skimmed dried milk with cereal and bean products, reinforced with calcium, iron and vitamins A and D, as a weaning diet. It is a pity, for the thread of the author's argument is interrupted by an irrelevant chapter mainly concerned with the provision of day nursery and nursery schools in different countries. May this booklet rouse the conscience of some among us who can help towards the better feeding of children in British colonies.

FILM REVIEWS

The Development of Manipulation. 16 mm., silent, monochrome, 20 minutes.

This new film made by Professor Illingworth is, like his film, 'The Development of Locomotion' based on Gesell's work. It shows what children can do with their hands at different ages. It is a very useful survey and should be found valuable for teaching.

Surprise Attack. 16 mm., sound, black and white, 10 minutes. Made by the Central Office of Information and Central Council for Health Education for the Ministry of Health. 1951. Distributed free by the Central Film Library.

This is a dramatic appeal to parents to have their children vaccinated in infancy. The public may draw the conclusion that mass vaccination is advocated but this is a small point. A reviewer must have his fun, and yours would criticize the medical officer of health for touching the face of a smallpox patient and then putting his hand in his pocket. The film is well made and medical students as well as parents will profit from seeing it.

Your Children's Play. 16 mm., sound, 20 minutes.

Your Children Walking. 16 mm., sound, 20 minutes. Made by the Central Office of Information in collaboration with the Central Council for Health Education for the Ministry of Health. 1951. Available from the Central Film Library.

These films are designed for showing in infant welfare centres and to parents' clubs and nursery school staffs.

Your Children's Play conveys a very good attitude towards play and toys. One hesitates a little before recommending it because it shows 'stupid' parents without conveying that they are more over-anxious, over-worked or uninformed, than essentially stupid. Despite this fault the film will be a very useful one.

Your Children Walking could have given more explanation in the way muscles and tendons act in the legs and feet and less time in telling parents to urge their children to adopt a good posture. The remaining advice is very good and the film will be useful for nurses as well as for parents.